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The Journal of Allergy

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The Journal of Allergy

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Original Articles

ON THE IDENTITY OF THE ATOPENS OF HIGH RAGWEED AND LOW RAGWEED POLLEN*

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LATE or autumnal hay fever in this locality is due, in the great majority of cases, to the pollens of high ragweed *(Ambrosia trifida)* and low ragweed *(Ambrosia artemisiaefolia)*. This has been proved countless times by many investigators, using extracts of these pollens made in a variety of ways and tested by intracutaneous or scarification methods. In 740 cases of late hay fever studied in 1926[1] by the intracutaneous method, ragweed pollen was found to be the only or chief cause in 696, or 94 per cent of the cases. Despite the botanical differences between the two ragweed plants, the physiologic effect of their pollens upon the ragweed-sensitive patient has been considered to be identical.

In over 800 cases of late hay fever tested in 1922 and 1923 by the intracutaneous and ophthalmic methods,[2] no patient was found who reacted to one ragweed pollen extract without reacting to the other. Brown,[3] in 1925, working with the extracts of high and low ragweed pollen separately, found, in a series of 31 cases of late hay fever, that each individual was equally sensitive to the two extracts. One-half of these cases were treated with high ragweed pollen extract alone, and one-half with the low ragweed pollen extract alone. Excellent clinical results, quite similar in the two groups, were obtained. Furthermore, these results were as successful as those obtained in the routine treatment where equal parts of the high and low ragweed pollen extracts were used for injection. When, with gradually ascending doses spread over a period of two or more months, the maximum tolerance had been established in these cases to the one extract, suddenly, with no preliminary adjustment, the equivalent or a larger dose of the other extract was given, without the development of any of

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those untoward symptoms certain to have followed the excessive initial injection of an unrelated pollen extract. Brown concluded that the atopens of the two pollens were identical.

Using the passive transfer method of Prausnitz and Küstner,[4] Coca and Grove[5] could demonstrate no differences in the atopens of the two ragweeds by the principle of specific exhaustion. Walzer and Grove,[6] using the Dale method, found that the uterine strip of the guinea pig, sensitized to either ragweed pollen, was equally reactive to both pollen extracts. Furthermore, desensitization to either pollen rendered the uterine strip insensitive to both. Their conclusions were that the atopens in the two varieties of ragweed were identical.

Rappaport and Johnson,[7] however, employing the scarification method in 40 cases of late hay fever, failed to show, in any instance, an equal degree of sensitiveness to the high and low ragweed pollen extract. They found that in half their cases the tests were quite negative to high ragweed pollen extract but positive to low ragweed pollen extract. In the other half, tests were moderately positive to the high ragweed pollen extract and definitely positive to the low ragweed pollen extract. It should be emphasized that their tests were made with various protein fractions and no mention is made of control tests with extracts of whole pollen. They also considered that in the high ragweed pollen only the albumin fraction was responsible for the positive reactions, while in the low ragweed pollen both globulin and albumin, but chiefly the former, caused the positive reactions.

In this present study, 183 cases of late hay fever were examined for sensitiveness to the high and low ragweed pollen extract. Three methods were employed: (1) parallel testing in hay fever subjects with the intracutaneous method; (2) specific exhaustion of passively sensitized skin sites, and (3) interchange of maximum pollen injections. The extracts used were made according to Coca's method[8] and were standardized by their nitrogen content.

PARALLEL TESTING

One hundred and six consecutive cases were tested intracutaneously with a mixed extract consisting of equal parts of high and low ragweed pollen extract. At a subsequent examination, each patient was tested with extracts of high and low ragweed pollen separately. Particular care was taken to see that equal amounts of the testing extracts were introduced into the skin. In no instance could there be demonstrated a marked positive reaction to one ragweed pollen extract alone—every case was positive to both, and usually to an equal degree. Furthermore, the reactions to the high and the low ragweed pollen extracts separately were no more and no less than the reactions obtained to the mixture of high and low ragweed pollen extract, employed at the first examination.

The ophthalmic reaction affords a most delicate test for slight degrees of variation in pollen sensitiveness. This test is made by instilling into the eye at the outer canthus, from the protected point of a needle, a drop of the extract under consideration. Within five to seven minutes a positive reaction is denoted by itching, injection of the inner canthus and conjunctiva, and sclera, the extent of the involvement determining the classification of the reaction. Where only the inner canthus is involved, the reaction is termed "slight." If the conjunctiva of the lower lid and the quarter segment of the sclera inferior to the iris is involved, the reaction is termed "slight to moderate," or "moderate"; if the conjunctiva and lower half of the sclera are affected, the reaction is termed "marked."

The ophthalmic test was accordingly studied in 77 additional cases of late hay fever together with intracutaneous tests. One eye, usually the right, was tested with high ragweed pollen extract; the other with low ragweed pollen extract.

The intracutaneous tests differed from those described in the series of cases mentioned above, in that each patient was tested quantitatively. In an effort to demonstrate very slight differences in the relative activity of the two ragweed pollens, this quantitative testing was done in each case with dilutions of the ragweed pollen extracts that varied but slightly in strength. These dilutions, twice as many as were used in routine testing, were as follows: 0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05 mg. N per c.c.

In no case so tested was there found a reaction to only one of the ragweed pollen extracts. In every instance reactions were obtained to both ragweed pollen extracts, high and low, and in both skin and eye. Furthermore, the reactions to the two pollen extracts were practically equal in all cases, by intracutaneous tests. By the ophthalmic test, slight variations in the degree of reaction to the two pollen extracts were noted, but these differences were of minor degree. (See Table I.)

EXHAUSTION BY PASSIVE TRANSFER

It has been shown conclusively by numerous investigators that the sera of hypersensitive individuals contain reacting antibodies capable of transferring temporary sensitiveness to the skin of normal individuals. These reacting antibodies are specific, rendering the normal individual sensitive only to the substances to which the patient by cutaneous test can be demonstrated to be hypersensitive. False positive and indeterminate reactions are not transferred. Due to this same characteristic of specificity, the reacting antibodies in the skin sites sensitized in the normal with the serum of the hypersensitive patient can be exhausted by repeated testing with one substance, without affecting the reactivity of the site to tests with other substances to which the patient is equally sensitive. Advantage has been taken of these facts

Table I

Protocol Showing Parallel Testing With the Extracts of High and Low Ragweed Pollen*

Chart No.	Intracutaneous reactions: High ragweed pollen extract 0.0001	0.0005	0.001	0.005	0.01	0.05	Intracutaneous reactions: Low ragweed pollen extract 0.0001	0.0005	0.001	0.005	0.01	0.05	Ophthalmic reactions: High ragweed pollen dilution	result	Ophthalmic reactions: Low ragweed pollen dilution	result
975	slt	mkd	mkd				slt	mod	mkd				0.005	slt	0.001	slt
67	mod	mkd	mkd				mkd	mkd	mkd				0.001	slt	0.001	slt-mod
6		slt	mod	mkd				slt	mod	mkd			0.01	slt	0.01	slt
516	mkd	mkd +	mkd ++				mkd	mkd +	mkd ++				0.001	slt	0.001	slt-mod
961		slt	mod	mod	mkd			slt	mod	mod	mkd		0.005	slt	0.005	slt
783	mod	mod	mkd				mod	mod	mkd				0.005	very slt	0.005	slt
30		slt	mod	mkd	mkd			slt	mod	mkd	mkd		0.01	slt	0.01	slt
863	slt	mod	mkd	mkd				slt	mod	mkd	mkd		0.01	slt	0.01	slt-mod
141		mod	mkd	mkd				mod	mkd	mkd			0.01	slt	0.01	slt
838		slt	mod	mkd				slt	mod	mkd			0.005	slt	0.005	slt
782		slt	mkd	mkd				slt	mkd −	mkd			0.01	slt	0.05	slt
423		slt	mod	mkd				slt	mkd −	mkd			0.05	slt	0.05	slt
653		slt	slt	mkd				slt	mod	mkd			0.001	slt	0.001	slt
338	mkd	mkd	mkd+				mkd	mkd	mkd +				0.001	slt	0.001	slt
826		slt	mod	mkd	mkd			mod	mkd	mkd	mkd		0.01	slt	0.01	slt
865		mod	mod	mkd				mod	mod	mkd			0.005	slt	0.005	slt
27	slt	mkd	mkd				slt	mod	mkd				0.01	slt	0.01	slt
117		slt	mod	mkd				slt	mod	mkd			0.01	slt	0.01	slt
439	mod	mod	mkd				mod	mod	mkd				0.001	slt	0.001	slt
8	slt	mod	mkd				slt	mod	mkd				0.01	slt	0.01	slt
873		slt	mod	mkd				slt	mod	mkd			0.01	slt	0.01	slt
568		slt	mod	mkd				slt	mod	mkd			0.01	slt	0.01	slt
667		slt	mod	mkd				slt	mod	mkd			0.005	slt	0.005	slt-mod
559	slt	mod	mkd	mkd			slt	slt	mkd	mkd			0.005	slt	0.005	slt
332			mod	mod	mkd				mod	mod	mkd		0.05	slt	0.05	slt

*The abbreviations "slt" (slight), "mod" (moderate), "mkd" (marked), and "mkd +" are employed to designate the reactions obtained by intracutaneous test. If the wheal is but slightly increased over its original size and with regular outline, it is considered "slight"; if it is of the same character but somewhat more active, it is considered "moderate"; if the wheal is several times the size of the original, with pseudopod outline, it is termed "marked." Any marked reaction, more than an inch in diameter, is called "marked +".

TABLE I—CONT'D

CHART NO.	INTRACUTANEOUS REACTIONS												OPHTHALMIC REACTIONS			
	HIGH RAGWEED POLLEN EXTRACT						LOW RAGWEED POLLEN EXTRACT						HIGH RAGWEED		LOW RAGWEED	
	0.0001	0.0005	0.001	0.005	0.01	0.05	0.0001	0.0005	0.001	0.005	0.01	0.05	POLLEN DILUTION	RESULT	POLLEN DILUTION	RESULT
36		slt	mod	mkd				slt	mod	mkd			0.01	slt-mod	0.01	slt-mod
234		slt	mod	mkd				slt	mod	mkd			0.01	slt	0.01	slt
921		slt	mod	mkd				slt	mod	mkd			0.005	slt-mod	0.005	slt-mod
694	mkd	mkd					mkd	mkd					0.005	slt-mod	0.005	slt-mod
31		slt	mod	mkd				slt	mod	mkd			0.05	slt	0.05	slt
592	mod	mod	mkd				mod	mod	mkd				0.01	slt	0.01	slt
180		slt	mod	mkd				slt	mod	mkd			0.01	slt	0.01	slt
24	mkd		mkd+				mkd		mkd +				0.001	slt	0.001	slt
53	slt	mod	mkd –		mkd		slt	mod	mkd +		mkd		0.005	slt	0.005	slt
918	slt	mod	mkd	mkd +			slt	mod	mkd –	mkd +			0.005	very slt	0.005	slt
883	mod	mkd					mkd	mkd					0.0005	very slt	0.0005	very slt
436	mkd	mkd					mkd	mkd					0.005	slt	0.005	slt
101	mkd	mkd	mkd				mkd	mkd	mkd				0.005	slt	0.005	slt
022			slt-mod	mkd –					slt-mod	mkd –			0.01	slt	0.01	slt
294			mod	mkd –					mod	mkd –			0.01	very slt	0.01	slt
398				slt	slt-mod	mkd				slt	slt	mkd	0.1	neg	0.1	neg
528	mkd	mkd						mkd	mkd				0.005	slt	0.005	slt
259	slt	mkd					mod	mod					0.001	slt	0.001	slt
081	mkd–	mkd	mkd+				mkd	mkd	mkd				0.005	very slt	0.005	very slt
875	mod	mkd						mod	mkd				0.005	slt-mod	0.005	slt
874		mkd –	mkd -	mkd					mod	mkd –	mkd		0.005	slt-mod	0.005	slt
995	mod	mkd					mod	mkd					0.005	slt	0.005	slt
320	mkd	mkd					mod	mkd					0.0005	slt-mod	0.0005	slt
653			slt	mkd					slt	mkd –			0.01	very slt	0.01	slt
605	mkd		mkd				mkd		mod				0.005	very slt	0.005	very slt

TABLE I—CONT'D

CHART NO.	INTRACUTANEOUS REACTIONS												OPHTHALMIC REACTIONS			
	HIGH RAGWEED POLLEN EXTRACT						LOW RAGWEED POLLEN EXTRACT						HIGH RAGWEED		LOW RAGWEED	
	0.0001	0.0005	0.001	0.005	0.01	0.05	0.0001	0.0005	0.001	0.005	0.01	0.05	POLLEN DILUTION	RESULT	POLLEN DILUTION	RESULT
241	mod		mkd+				mod		mkd +				0.005	mod	0.005	slt
336		mkd	mkd					mkd +	mkd				0.005	slt	0.005	slt
603	mkd	mkd+					mkd	mkd +					0.0005	slt	0.0005	slt
411	mod	mkd –	mkd				mod	mkd –	mkd				0.001	very slt	0.001	very slt
432	mkd	mkd					mkd	mkd					0.005	slt	0.005	slt
441	slt	mod	mkd –	mkd			slt	mod	mkd –	mkd			0.005	slt	0.005	slt-mod
772	mkd –	mkd					mkd –	mkd					0.001	slt	0.001	slt
807	mkd –	mkd					mkd –	mkd					0.001	slt	0.001	slt
498	mod	mkd	mkd				mod	mod	mkd				0.001	slt	0.001	slt
564	mkd	mkd+					mkd	mkd +					0.001	slt	0.005	very slt
709	mod	mkd+					mod	mkd					0.005	slt	0.005	slt
584	slt	mkd+	mkd				slt	mkd –	mkd				0.005	slt	0.005	slt
675		mkd	mkd					mod	mkd				0.05	slt	0.01	slt
477	slt	mod	mkd				slt	mod	mkd				0.01	slt	0.005	slt
426			mkd	mkd					mkd	mkd +			0.005	slt	0.005	slt
737	mod	mkd	mkd				mkd	mkd	mkd				0.001	slt	0.001	slt
601	mkd		mkd+				mkd		mkd +				0.0005	slt	0.001	slt
492			mod	mkd +	mkd –	mkd			slt-mod	mkd –	mkd –	mkd	0.1	very slt	0.1	very slt
753	mkd –	mkd					mkd	mkd					0.001	slt	0.001	slt
635	mkd	mkd					mkd	mkd					0.0005	slt	0.0005	slt
703	mod	mod	mkd				mod	mod	mkd				0.001	very slt	0.001	very slt
622	slt	mkd					mod	mkd					0.0005	slt	0.005	slt
355	mkd –	mkd					mkd –	mkd					0.0005	slt	0.0005	slt-mod
665	slt-mod	mkd	mkd				slt	mkd	mkd				0.001	very slt	0.001	very slt
624	mkd	mkd					mkd	mkd					0.001	slt	0.005	slt
781	mod	mod	mkd				mod	mod	mkd				0.01	slt	0.01	slt
513	mod	mkd					mkd	mkd					0.005	slt	0.005	very slt

in an attempt to determine the identity of the reacting antibodies to the high and low ragweed pollen excitants.

The sera studied were obtained from 9 patients with late hay fever who showed marked positive reactions to an equal degree upon intracutaneous test with high and low ragweed pollen extract. Of these, 5 patients were of Class B, 1 of Class AB, and 1 of Class C.* The remaining 2 patients were very sensitive, being grouped in Class A. To afford a proper control, patients were selected that were also sensitive, by intracutaneous tests, to timothy pollen extract. These patients were also clinically sensitive to this pollen, giving a history of early hay fever.

The blood specimen obtained from each patient by venipuncture was defibrinated by whipping, centrifuged, and the supernatant serum removed. This was sterilized by Berkefeld filtration and stored aseptically without preservative. In the majority of cases, the serum was used within forty-eight hours of collection, although it has been shown[9] that the reacting antibodies in such serum usually remain potent for months.

The recipients selected for the serum sites were normal individuals, with no demonstrable hypersensitiveness, and were negative by intracutaneous test to the pollens under consideration. Each site was sensitized by injecting intracutaneously 0.1 c.c. of serum. With each serum, five such sites were prepared, these being placed in a single row, down the lateral aspect of the upper arm, at intervals of at least 1½ inches. Only one row was placed in each arm. After an interval of twenty-four hours, the sites were tested intracutaneously (see Table II).

In each instance,† Site 1 was tested with high ragweed pollen extract 0.01. A marked positive reaction was obtained as indicated by a wheal formation with pseudopods, surrounded by a definite zone of erythema. After twenty-four hours the test was repeated in the same site with the same extract of high ragweed pollen 0.01. A positive reaction resulted, being slight in the case of two sera and moderate in the case of five. After twenty-four hours a repetition of the test in the same site gave negative results, indicating the exhaustion of Site 1 to the reacting antibodies of high ragweed pollen. No reaction having developed by the end of twenty minutes, Site 1 was then tested with the low ragweed pollen extract 0.01 with negative results, showing the absence of special reacting antibodies to this pollen. After an interval of twenty minutes, the same site, tested with timothy

*NOTE: The classification here employed is that described by VanderVeer, Cooke and Spain, American Journal Medical Science **174**: 101, 1927. Class A subjects are considered extremely sensitive, developing upon intracutaneous test a marked reaction to a dilution of 0.0001 mg. N per c.c. and a marked plus reaction to a dilution of 0.001 mg. N per c.c. A reaction is considered "marked plus" when it consists of a wheal with pseudopods, which is more than an inch in diameter. Class B subjects develop a marked reaction to a dilution of 0.001 and a marked plus to 0.01. Class C subjects are of average sensitiveness, developing a moderate reaction to 0.001 and a marked reaction to 0.01.

†The exception to this is Serum 3 where 0.05 dilutions were used in each test instead of 0.01.

TABLE II

SPECIFIC EXHAUSTION OF THE REACTING ANTIBODIES OF HIGH RAGWEED POLLEN EXTRACT AND LOW RAGWEED POLLEN EXTRACT IN THE SERA OF SEVEN CASES OF LATE HAY FEVER

SERUM					24 HR. LATER		24 HR. LATER		20 MIN. LATER		20 MIN. LATER	
NUMBER	CLASSIFICATION OF SENSITIVENESS	SITE	TEST	RESULT	TEST	RESULT	TEST	RESULT	TEST	RESULT	TEST	RESULT
1	High Ragweed, Class B	1	HR 0.01	mkd	HR 0.01	mod	HR 0.01	neg	LR 0.01	neg	T 0.01	mkd
	Low Ragweed, Class B	2					HR 0.01	mkd				
	Timothy, Class B	3	LR 0.01	mkd	LR 0.01	mod	LR 0.01	neg	HR 0.01	neg	T 0.01	mkd
		4					LR 0.01	mkd				
		5	T 0.01	mkd	T 0.01	slt	T 0.01	neg	HR 0.01	mkd		
2	High Ragweed, Class AB	1	HR 0.01	mkd	HR 0.01	mod	HR 0.01	neg	LR 0.01	neg	T 0.01	mod
	Low Ragweed, Class AB	2					HR 0.01	mkd				
	Timothy, Class B	3	LR 0.01	mkd	LR 0.01	mod	LR 0.01	neg	HR 0.01	neg	T 0.01	mkd
		4					LR 0.01	mkd				
		5	T 0.01	mkd	T 0.01	mod	T 0.01	neg	LR 0.01	mkd		
3	High Ragweed, Class C	1	HR 0.05	mkd	HR 0.05	mod	HR 0.05	neg	LR 0.05	neg	T 0.01	mkd
	Low Ragweed, Class C	2					HR 0.05	mkd				
	Timothy, Class C	3	LR 0.05	mkd	LR 0.05	mod	LR 0.05	neg	HR 0.05	neg	T 0.01	mkd
		4					LR 0.05	mkd				
		5	T 0.05	mkd	T 0.05	mod	T 0.05	neg	HR 0.05	mkd		

TABLE II—CONT'D

SERUM NUMBER	CLASSIFICATION OF SENSITIVENESS	SITE	TEST	RESULT	24 HR. LATER TEST	24 HR. LATER RESULT	24 HR. LATER TEST	24 HR. LATER RESULT	20 MIN. LATER TEST	20 MIN. LATER RESULT	20 MIN. LATER TEST	20 MIN. LATER RESULT
4	High Ragweed, Class B	1	HR 0.01	mkd	HR 0.01	mod	HR 0.01	neg	LR 0.01	neg	T 0.01	mod
	Low Ragweed, Class B	2					HR 0.01	mkd				
	Timothy, Class B	3	LR 0.01	mkd	LR 0.01	mod	LR 0.01	neg	HR 0.01	neg	T 0.01	mkd
		4					LR 0.01	mkd				
		5	T 0.01	mkd	T 0.01	slt	T 0.01	neg	LR 0.01	mkd		
5	High Ragweed, Class B	1	HR 0.01	mkd	HR 0.01	slt	HR 0.01	neg	LR 0.01	neg	T 0.01	mod
	Low Ragweed, Class B	2					HR 0.01	mkd				
	Timothy, Class B	3	LR 0.01	mkd	LR 0.01	slt	LR 0.01	neg	HR 0.01	neg	T 0.01	mod
		4					LR 0.01	mkd				
		5	T 0.01	mkd	T 0.01	slt	T 0.01	slt	LR 0.01	mkd		
6	High Ragweed, Class B	1	HR 0.01	mkd	HR 0.01	mod	HR 0.01	neg	LR 0.01	neg	T 0.01	mkd
	Low Ragweed, Class B	2					HR 0.01	mkd				
	Timothy, Class B	3	LR 0.01	mkd	LR 0.01	mod	LR 0.01	neg	HR 0.01	neg	T 0.01	mkd
		4					LR 0.01	mkd				
		5	T 0.01	mkd	T 0.01	mod	T 0.01	neg	HR 0.01	mkd		
7	High Ragweed, Class B	1	HR 0.01	mkd	HR 0.01	slt	HR 0.01	neg	LR 0.01	neg	T 0.01	mkd
	Low Ragweed, Class B	2					HR 0.01	mkd				
	Timothy, Class B	3	LR 0.01	mkd	LR 0.01	slt	LR 0.01	neg	HR 0.01	neg	T 0.01	mod
		4					LR 0.01	mkd				
		5	T 0.01	mkd	T 0.01	slt	T 0.01	neg	LR 0.01	mkd		

TABLE III

SPECIFIC EXHAUSTION OF THE REACTING ANTIBODIES OF HIGH RAGWEED POLLEN EXTRACT AND LOW RAGWEED POLLEN EXTRACT IN TWO CLASS A SERA

SERUM	SITE	TEST	RESULT	24 HR. LATER		24 HR. LATER		24 HR. LATER		20 MIN. LATER		20 MIN. LATER	
				TEST	RESULT	TEST	RESULT	TEST	RESULT	TEST	RESULT	TEST	RESULT
H	1	HR 0.01	mkd	HR 0.01	mkd	HR 0.01	mod	HR 0.01	slt	LR 0.01	slt	T 0.01	mkd
	2									LR 0.01	mkd		
	3	LR 0.01	mkd	LR 0.01	mkd	LR 0.01	mod	LR 0.01	slt	HR 0.01	slt	T 0.01	mkd
	4									HR 0.01	mkd		
	5	T 0.01	mkd	T 0.01	mkd	T 0.01	mkd	T 0.01	slt	HR 0.01	mkd		
I	1	HR 0.01	mkd	HR 0.01	mkd	HR 0.01	mkd	HR 0.01	neg	LR 0.01	neg	T 0.01	mkd
	2									LR 0.01	mkd		
	3	LR 0.01	mkd	LR 0.01	mkd	LR 0.01	mkd	LR 0.01	neg	HR 0.01	neg	T 0.01	mkd
	4									HR 0.01	mkd		
	5	T 0.01	mkd	T 0.01	mkd	T 0.01	mod	T 0.01	neg	HR 0.01	mkd		

pollen extract 0.01 developed a definitely positive reaction, indicating the presence in the site of the reacting antibodies to timothy pollen. Site 2 was used as a control, being tested for the first time on the third day, with high ragweed pollen extract 0.01, the resulting positive reaction indicating that the negative result obtained in Site 1 upon this day with high ragweed pollen extract 0.01 was not due merely to a dissipation of the reacting antibodies into the tissues of the recipient.

In each instance, Site 3 was tested with low ragweed pollen extract 0.01 according to the same method used in Site 1. The results were similar, showing that this site exhausted to low ragweed pollen extract would not react to high ragweed pollen extract, but would do so to the timothy pollen extract. Site 4 was a control similar to Site 2. Site 5 was tested with timothy pollen extract 0.01 in the manner employed with high and low ragweed pollen extract in Sites 1 and 3. Exhaustion to timothy pollen extract did not affect the reaction to high or low ragweed pollen extract.

Two very sensitive sera were also studied. These were taken from patients giving marked plus reactions upon being tested intracutaneously with high ragweed pollen extract 0.001, low ragweed pollen extract 0.001 and timothy pollen extract 0.001, being therefore grouped as Class A cases. As seen in Table III, the results with these sera differed from those described above only in the fact that a period of time, longer by twenty-four hours, was necessary to exhaust the serum sites.

The exhaustion, therefore, accomplished in the serum sites to high ragweed pollen extract, or to low ragweed pollen extract was always apparently complete. There was in no instance any suggestion of a partial exhaustion, such as would occur if the reacting antibodies of the two ragweed pollens were similar, but not identical. That this exhaustion was specific and not due to tissue fatigue was proved by the ease with which positive reactions to tests with timothy pollen extract could be obtained after the several ragweed tests were made.

INTERCHANGE OF MAXIMUM POLLEN INJECTIONS

Thirteen cases of late hay fever, varying from Class A to Class C, were selected at random for this phase of the study (Table IV). The duration of treatment before the onset of symptoms varied from twelve weeks in one patient to two weeks in another. A phylactic case, reporting for treatment after the onset of symptoms, was included. Eight cases were treated with high ragweed pollen extract alone, 5 with low ragweed pollen extract alone. The results of treatment were similar and compare favorably with those obtained with a mixture of equal parts of high and low ragweed pollen extract. Near the end of the season, seven days after the maximum dose for each patient had been reached, and at the time the next injection was due,

TABLE IV

INTERCHANGE OF MAXIMUM POLLEN INJECTIONS IN THIRTEEN LATE HAY FEVER CASES

CHART NO.	CLASS	AGE	SEX	INITIAL INJECTION		LAST INJECTION BEFORE INTERCHANGE		INTERCHANGED INJECTION		REACTION		RESULT OF SEASON'S TREATMENT
				DATE GIVEN	AMOUNT	DATE GIVEN	AMOUNT	DATE GIVEN	AMOUNT	MARKED LOCAL	CONSTITUTIONAL	
755	B	63	F	June 7, 1929	LR 0.0002	Sept. 13, 1929	LR 0.03	Sept. 20, 1929	HR 0.03	None	None	80% Improvement
764	C	49	M	June 28, 1929	LR 0.0002	Sept. 13, 1929	LR 0.03	Sept. 20, 1929	HR 0.03	None	None	90% Improvement
771	B	26	M	July 22, 1929	LR 0.0002	Sept. 9, 1929	LR 0.007	Sept. 16, 1929	HR 0.007	None	None	90% Improvement
773	B	48	M	July 26, 1929	LR 0.0002	Sept. 16, 1929	LR 0.015	Sept. 23, 1929	HR 0.015	None	None	50% Improvement
758	B	58	M	June 10, 1929	LR 0.0002	Sept. 16, 1929	LR 0.03	Sept. 23, 1929	HR 0.03	None	None	90% Improvement
750	B	42	F	June 3, 1929	LR 0.0002	Sept. 16, 1929	LR 0.007	Sept. 23, 1929	HR 0.007	None	None	50% Improvement
787	B	31	M	Aug. 12, 1929	LR 0.0002	Sept. 13, 1929	LR 0.007	Sept. 23, 1929	HR 0.007	None	None	50% Improvement (Phylactic)
344	B	31	M	July 8, 1929	LR 0.0002	Sept. 9, 1929	LR 0.01	Sept. 16, 1929	HR 0.01	None	None	80% Improvement
757	C	38	M	June 10, 1929	HR 0.0002	Sept. 13, 1929	HR 0.07	Sept. 20, 1929	LR 0.07	None	None	80% Improvement
745	A	22	M	June 10, 1929	HR 0.0001	Sept. 9, 1929	HR 0.008	Sept. 16, 1929	LR 0.008	None	None	90% Improvement
694	B	21	F	June 10, 1929	HR 0.0002	Sept. 9, 1929	HR 0.05	Sept. 16, 1929	LR 0.05	None	None	No improvement*
751	C	34	M	June 10, 1929	HR 0.0002	Aug. 30, 1929	HR 0.05	Sept. 16, 1929	LR 0.05	None	None	75% Improvement
754	A	47	M	June 14, 1929	HR 0.00005	Sept. 13, 1929	HR 0.01	Sept. 20, 1929	LR 0.01	None	None	80% Improvement

*A chronic bilateral antrum infection found in this patient.

there was given an injection equal in amount to the one last administered, but of the other ragweed pollen extract. In no instance was there the slightest indication of overdosage, such as would be sure to have occurred had the injection consisted of an unrelated pollen extract. This finding is in entire accord with the results of Brown.[3]

DISCUSSION

In their effort to identify different protein fractions of the pollen extracts as the excitants of the hypersensitiveness in hay fever, Rappaport and Johnson have strangely disregarded the experiments of Grove and Coca,[10] in which it was shown that the atopic excitant remained in undiminished activity in the solution after complete removal of the proteins by digestion and dialysis.

The discordant results obtained by Rappaport and Johnson[8] were doubtless due to the different effects of the chemical procedures they were using upon the excitant in the two pollens. This is evidenced by the fact that the differences in the two preparations were all in one direction, namely, to the disparagement of the preparation from the high ragweed pollen. The results obtained by these authors with the chemically isolated derivatives of the pollens could not be accepted without consistent confirmation of their reported differences, as would be the case also if the tests had been made with the original extracts of the two pollens.

CONCLUSIONS

The foregoing study on a large number of patients, in agreement with many previous observations of others, has failed to reveal any specific difference in the atopens of the pollens of high and low ragweed.

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THE DETERMINATION OF FACTORS TO EXPLAIN MARGINAL FAILURE IN HAY FEVER DESENSITIZATION*

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THAT hay fever is an important clinical entity deserving of our utmost attention and study, can easily be deduced from the reports tending to show that the victims of that disease in the United States number over one million. It is of further interest and marked importance for the reason that, as Balyeat[1] states, fully 65 per cent of hay fever sufferers develop asthma.

The problem now is not only how effectively to treat the hay fever subject, but more so, how to treat him to the end of obtaining absolute therapeutic results. Many seasonal victims apparently accept as valueless a regimen of therapeusis that produces less than 90 to 100 per cent successful results. That a certain percentage of hay fever patients remains unaided by the treatment received, is not entirely unknown to the public suffering from that malady. We, within the ranks, know, too, that even in the hands of men well trained in this particular specialty, there is that varying marginal percentage of failure.

Spivacke[2] reported 35.9 per cent complete relief from symptoms in the treatment of 114 patients during the season of 1924. Of these, 40.4 per cent received marked relief, but 10.5 per cent received slight or no relief whatsoever. More recently, Ramirez[3] in his statistical studies on the treatment of hay fever clearly showed the definite occurrence of marginal failure, even in well-managed and well-controlled hay fever therapy. Even Balyeat,[4] whose figures as to good results are unusually high and whose cases are well controlled, reported 6 per cent of cases as receiving less than 50 per cent improvement and 31.2 per cent of cases as receiving elimination of only 80 per cent of their hay fever symptoms.

The question arises as to what accounts for the marginal failure in pollen-sensitive subjects who have received proper, thorough, and maximum desensitization.

Feinberg[5] discussed the various methods that should be employed in order that the percentage of good results in hay fever treatment become considerably augmented. He mentioned the necessity of preseasonal combined with co-seasonal treatment, along with the individualization of dosages of pollen. He also mentioned as factors, the

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careful determination of species of pollen to be used, and the preservation of the potency of the pollen by refrigeration in concentrated form. No mention, however, was made of the possibility of a complicated extrapollen hypersensitivity untreated, as a contributory factor.

Cohen and his associates,[6] in discussing the causes of *Failure in the Treatment of Hay Fever,* outlined the important factors involved in about the same manner as cited above. In outline form it was explained that failure is due mainly to: "(1) incorrect diagnosis; (2) inadequate or improper treatment; (3) inability of the patient's body to develop a tolerance to pollen extract injections, and (4) contact with unusually large doses of pollen." These authors also mentioned, in passing, that "Sometimes there is a coexisting sensitivity to some substances other than pollen, which may exacerbate the symptoms during the hay fever season."

Similarly, Balyeat[4] mentioned that many seasonal pollen hay fever cases are not only multiply sensitive to pollen, but are also sensitive to other proteins, such as orris root, animal epithelia, etc. He further stated that multiple sensitivity to pollen is not given the consideration by the majority that it should receive, and that the lack of such consideration is the cause of many failures in pollen therapy. He did not, however, dwell on the probability that the poor results may, in part, be due to a failure to determine the extra-pollen sensitivity and the failure to institute desensitization.

In my opinion, a hypersensitivity to certain protein substances, other than pollens, in contact with the patient in question, is responsible for the continued reactivity. I believe, too, that the pollen sensitivity is enhanced by the hypersensitivity to those proteins, and that the latter is therefore responsible for the increased reactivity. This, I believe, is borne out by the fact that many of the patients will tell of manifold circumstances and of numerous substances by which and through which their hay fever symptoms became greatly aggravated. Behind all of that can clearly be seen, in those instances, a sensitivity to allergens other than pollens.

A few case reports will serve to illustrate the statements herein presented.

CASE 1.—A. S., a woman, aged forty years, was found sensitive to the ragweed pollens. This coincided with the clinical history that she gave. She received maximum desensitization long before the onset of the late hay fever season. This patient on August 25 and on many subsequent days, remained free from hay fever symptoms. To prove to her own satisfaction that she had built up a resistance against the fall pollens, she went out in the country one day in the midst of areas stocked with ragweed. She suffered no untoward results. This she had never been able to do heretofore. The same evening, however, as she busied herself with housework, removing the dusty curtains from the windows, a severe attack of hay fever developed which lasted many days. I tested her with inhalants and foods. I found the principal allergen to be dust (4 plus). She was then given frequent injections

of stock dust extract along with her pollen treatment. Her condition cleared up. She remained symptom-free throughout the rest of the season.

CASE 2.—A. W., male, aged thirty-five years, a cutter on clothing by occupation, was found sensitive to the fall pollens. He began his treatments three months before the usual onset of his symptoms. He was worked up completely, as regards the individualization of the pollens and was given a careful course of treatment of potent material. He reacted severely to the slightest overdosage and was therefore watched carefully against undue reactions. When the late hay fever season arrived, the patient reported only slight improvement. He was still very uncomfortable and his greatest discomfort was experienced while at work.

One day he was given as his allotment of work the cutting of woolens. He soon experienced a most violent seizure of hay fever. He had intelligence enough to insist that the material be removed from his table, and his symptoms immediately ceased. He was then tested with inhalants and foods and was found to be a multiply sensitive patient. Wool was a principal reactor. Institution of the proper precautions brought about 90 per cent improvement in his hay fever symptoms.

Similarly, Phillips[7] in his article on *Orris Root Coryza*, mentioned: two school girls, aged nine and eleven respectively, who had been completely protected from hay fever for many years by pollen therapy. One summer, however, they had to have, in addition, injections of orris extract, in order to obtain complete relief.

Vaughan[8] writing on the subject of *Pollinosis* impresses us with the idea that although hay fever may appear to be a purely local sensitization reaction, it should also be considered systemic, and the general or systemic point of view should determine the method of treatment. Vaughan lays before us four hypotheses on the subject at large. In his fourth postulate he states the following:

"In a person with pollinosis, there may be a coexistent sensitization to some protein which would not cause the symptoms of hay fever, but the reaction to which, superimposed on the pollen reaction, enhances the manifestation of the latter."

My own ideas on the subject are in accord with that of Vaughan. In our own clinic, we have observed about 10 per cent of hay fever subjects who were entirely unrelieved by the course of treatment, and about 30 per cent with but partial relief. In those showing not any to only partial relief, a study as to extrapollen hypersensitivity was undertaken for the purpose of this paper. There was also the object in view of instituting immediate desensitization or removal of contact with the offending allergen, if possible, and thus an attempt to bring about absolute freedom from symptoms.

A parallel series of patients who had received thorough and maximum desensitization, and who had reported complete relief, was taken at random for comparison. These, too, were given routine tests with inhalants and foods, and the results of the two groups (Tables I and II) are given for comparison.

TABLE I

THE OCCURRENCE OF SKIN REACTIONS TO ALLERGENS OTHER THAN POLLENS IN TWENTY HAY FEVER SUBJECTS WHO OBTAINED SLIGHT OR NO IMPROVEMENT FROM POLLEN TREATMENT

A. INHALANT PROTEINS	NO. OF PATIENTS GIVING NO REACTION	PER CENT INCIDENCE	NO. OF PATIENTS GIVING 1+ REACTION	PER CENT INCIDENCE	NO. OF PATIENTS GIVING 2+ REACTION	PER CENT INCIDENCE	NO. OF PATIENTS GIVING 3+ REACTION	PER CENT INCIDENCE	NO. OF PATIENTS GIVING 4+ REACTION	PER CENT INCIDENCE	TOTAL NUMBER REACTING	TOTAL PER CENT REACTING
Dust	4	20	0	0	7	35	6	30	3	15	16	80
Orris root	4	20	2	10	10	50	2	10	2	10	14	70
Horse	3	15	3	15	5	25	7	35	2	10	14	70
Feathers	6	30	2	10	5	25	4	20	3	15	12	60
Insecticide	5	25	3	15	7	35	2	10	3	15	12	60
Sheep	9	45	0	0	8	40	2	10	1	5	11	55
Rabbit	9	45	2	10	3	15	4	20	2	10	9	45
Cat	8	40	5	25	4	20	3	15	0	0	7	35
B. FOOD PROTEINS												
Meats	5	25	0	0	8	40	6	30	1	5	15	75
Wheat	6	30	0	0	8	40	5	25	1	5	14	70
Spices	4	20	2	10	11	55	3	15	0	0	14	70
Nuts	6	30	2	10	7	35	5	25	0	0	12	60
Oats	8	40	1	5	8	40	3	15	0	0	11	55
Beverages	5	25	5	25	6	30	3	15	1	5	10	50
Corn	8	40	1	5	8	40	1	5	0	0	9	45
Rye	7	35	5	25	4	20	3	15	1	5	8	40
Eggs	12	60	1	5	6	30	1	5	0	0	7	35
Vegetables	17	85	3	15	0	0	0	0	0	0	0	0

NOTE: Patients graded one plus are not included in the reacting group.

TABLE II

THE OCCURRENCE OF SKIN REACTIONS TO ALLERGENS OTHER THAN POLLEN IN TWENTY HAY FEVER SUBJECTS WHO OBTAINED 90 TO 100 PER CENT IMPROVEMENT FROM THE POLLEN TREATMENT

A. INHALANT PROTEINS	NO. OF PATIENTS GIVING NO REACTION	PER CENT INCIDENCE	NO. OF PATIENTS GIVING 1+ REACTION	PER CENT INCIDENCE	NO. OF PATIENTS GIVING 2+ REACTION	PER CENT INCIDENCE	NO. OF PATIENTS GIVING 3+ REACTION	PER CENT INCIDENCE	NO. OF PATIENTS GIVING 4+ REACTION	PER CENT INCIDENCE	TOTAL NUMBER REACTING	TOTAL PER CENT REACTING
Dust	9	45	7	35	1	5	1	5	1	5	3	15
Orris root	13	65	6	30	1	5	0	0	0	0	1	5
Horse	14	70	5	25	1	5	0	0	0	0	1	5
Feathers	18	90	2	10	0	0	0	0	0	0	0	0
Insecticide	18	90	2	10	0	0	0	0	0	0	0	0
Sheep	19	95	1	5	0	0	0	0	0	0	0	0
Rabbit	18	90	2	10	0	0	0	0	0	0	0	0
Cat	17	85	3	15	0	0	0	0	0	0	0	0
B. FOOD PROTEINS												
Meats	10	50	8	40	2	10	0	0	0	0	2	10
Wheat	16	80	1	5	2	10	1	5	0	0	3	15
Spices	15	75	3	15	2	10	0	0	0	0	2	10
Nuts	9	45	8	40	3	15	0	0	0	0	3	15
Oats	17	85	1	5	1	5	1	5	0	0	2	10
Beverages	14	70	3	15	3	15	0	0	0	0	3	15
Corn	19	95	1	5	0	0	0	0	0	0	0	0
Rye	18	90	2	10	0	0	0	0	0	0	0	0
Eggs	18	90	2	10	0	0	0	0	0	0	0	0
Vegetables	20	100	0	0	0	0	0	0	0	0	0	0

NOTE: Patients graded one plus are not included in the reacting group.

ANALYSIS OF CASES

Table IA is a record of the skin reactions to allergens of the inhalant group, other than pollens, in hay fever subjects who had received a proper and thorough course of treatment. These patients were treated in the usual manner with potent pollen material pre-seasonally and in part co-seasonally up to the time of the commencement of this clinical study. They were then observed to suffer severe symptoms of hay fever, at a time when the results from the pollen treatment should have become manifest. The order in which the protein substances are listed in this table is the order of frequency of hypersensitivity to these substances found in our patients. The allergens here listed are, in most instances, actually group representatives.

The average hypersensitivity for the group as a whole, considering mainly the first five principal reactors; namely, stock dust, orris root, animal epithelia, and insecticides, can be seen to be as high as 70 per cent. As soon as the sensitivity to these allergens was determined, proper advice and added treatment were immediately instituted. The results obtained were excellent. All reported marked improvement in from five to ten days, with practically no relapse of symptoms.

Table IB similarly records the results of the intradermal tests with allergens of the food protein group in hay fever subjects who, having resorted to pollen therapy, had obtained partial or no improvement whatsoever. Similarly here, the order of frequency as to sensitivity and dominant reaction encountered, is the order in which the food proteins are charted. Group representation is mainly the keynote in this list. The average sensitivity to the food proteins in our subjects, counting the first five dominant allergens, is also close to 70 per cent for the group.

The elimination from the diet of those patients, of such foods as were found by the tests to represent offending agents, soon made itself evident by a marked improvement in the hay fever symptoms.

Table IIA and B speaks for itself. It tends to show that in the 20 hay fever subjects who obtained excellent results from the treatment, and were taken at random from a large number of such cases for comparison, extrapollen hypersensitivity was found negligible. It should be mentioned that in the few where moderate to marked hypersensitivity was disclosed by the tests, close questioning revealed that contact with the particular offending agents did not exist. This explains why there was no interference with the pollen-treatment results.

I firmly believe, therefore, that extrapollen hypersensitivity, if present to a marked degree, obstructs the task to complete and successful pollen desensitization.

THE RELATION THAT EOSINOPHILIA BEARS TO THE TYPE OF SENSITIZATION

Brown[9] has shown that the eosinophile average for the food-sensitive patients is about 7 per cent., for the animal epidermal sensitive patients, exactly 6.5 per cent, and for the pollen-sensitive patients, about 6.5 per cent.

The question arises as to whether one finds an appreciable difference in the eosinophile percentage of the blood in the two classes of patients here presented; the pollen-sensitive subjects and those showing both pollen and extrapollen sensitivity. Is there an increase in the latter? Also, perhaps one should determine whether or not there exists an increase of eosinophiles in the blood in those manifesting hay fever symptoms as compared with those who are symptom-free.

Sternberg[10] suggested that the increase of eosinophiles in hay fever seems to be a shock reaction. He calls attention to the fact that he did not observe an increase in patients free from symptoms before and during their treatment, but that an increase did occur during the symptoms of hay fever.

Table III lists the class of patients who obtained partial or no improvement from the pollen desensitization and who were found to possess some form of extrapollen sensitivity, as evidenced by the skin reactions. The average eosinophilia in these subjects was found to be about 6 per cent.

TABLE III

EOSINOPHILIA IN POLLEN AND EXTRAPOLLEN SENSITIVE SUBJECTS. PATIENTS WERE MANIFESTING HAY FEVER SYMPTOMS

NAME	AGE YEARS	SEX	EOSINOPHILE PERCENTAGE
W. B.	39	M	10
M. E.	52	M	1
L. F.	50	M	9
J. F.	29	M	16
L. U.	52	M	2
J. L.	33	F	1
N. K.	42	M	9
A. S.	39	M	2
N. S.	28	M	3
A. W.	30	M	4
N. Z.	42	M	3
N. K.	22	M	3
E. R.	47	F	13
A. G.	22	F	11
I. G.	21	M	3
C. G.	48	F	9
S. S.	40	F	6
M. G.	30	F	5
A. R.	43	F	6
A. L.	46	F	5

Average eosinophile count = about 6 per cent

TABLE IV

EOSINOPHILIA IN HAY FEVER SUBJECTS SENSITIVE TO POLLEN ONLY. PATIENTS WERE FREE FROM SYMPTOMS

NAME	AGE YEARS	SEX	EOSINOPHILE PERCENTAGE
A. A.	50	M	6
A. B.	31	M	1
M. H.	35	F	2
J. B.	37	M	10
D. K.	35	F	19
J. K.	42	M	4
H. L.	38	M	2
B. L.	30	M	10
L. R.	35	F	3
F. R.	26	F	5
H. R.	28	F	2
S. R.	40	F	1
C. S.	46	F	0
J. S.	56	M	6
M. S.	50	M	1
J. S.	38	F	6
F. P.	42	F	9
S. T.	48	F	7
H. B.	30	M	1
A. S.	36	F	2

Average eosinophile count = 4.85 per cent

Table IV lists the class found to be sensitive to pollen only, as evidenced by the intradermal tests, and who obtained excellent results from their hay fever course of treatment. They were symptom-free subjects. The average eosinophile count here was found to be 4.85 per cent. Apparently then there is no connection between the type of sensitization and the percentage of eosinophiles in the blood.

In this study, the examination of the blood was made, for both classes, during the hay fever season. Apparently, in that case no great difference seems to exist between the presence or absence of symptoms and the percentage of eosinophiles in the blood. Age and sex were about equally distributed in both classes.

DISCUSSION

The group of extrapollen hypersensitive cases given here were hay fever subjects who had received the proper course of treatment, but still found themselves entirely unaided or only partially relieved from their symptoms. The group given is small, because extreme care was taken to make absolutely certain that no other factors could possibly enter to explain the causes of failure. Patients not having had maximum desensitization or those whose replies and histories could not be relied on were excluded from the group.

When the offending proteins had been found and their proper evaluation as to how much a causative factor each was had been assigned, they were eliminated from the diet and surroundings. Absolute relief from symptoms was thus secured. This proves to me that we have something to consider when we find an associated marked extrapollen sensitization in patients who fail to respond to the pollen treatment. Add to that the striking fact that, as herewith shown, an equal number of cases taken at random from a large group of patients reporting excellent results from the treatment, definitely failed to show any other hypersensitivity except to that of pollen, as evidenced by the skin reactions. The conclusion seems fairly drawn, that apparently the extrapollen sensitization factor had interfered with the results for complete relief from symptoms.

It is therefore urged that all seasonal hay fever patients be tested routinely with the inhalant and food proteins. The presence of sensitivity to the latter calls for treatment. The *Ideal Asthma Clinic*,[11] recently described, must add this procedure to its routine.

SUMMARY

1. It is generally known that a varying percentage of marginal failure in hay fever desensitization exists even in the hands of men well trained in their particular speciality. In our own clinic we found 10 per cent of cases resulting in complete failure to obtain relief from

their symptoms, and 30 per cent of cases as receiving only partial alleviation from their suffering.

2. Various explanations have been given as the causes for the failure. Practical suggestions of all kinds have been offered by others for the purpose of augmenting considerably the percentage of good results in hay fever treatment. The pursuance of these suggestive measures helped results to a certain degree, but not sufficiently to eradicate entirely the marginal existence.

3. Many writers have previously hinted at the probable coexistence of sensitization to some substances other than pollen, which may be responsible for the exacerbation of symptoms during the hay fever season. No data, however, have hitherto been compiled on that score.

4. In a number of cases, carefully chosen, showing not any to partial relief, a study of extrapollen sensitivity was undertaken for the purpose of determining whether or not that might be taken to account for the nonresponse to the treatment. For comparative purposes, the results of such sensitization tests in a parallel series of patients who obtained excellent results from the pollen treatment are also tabulated herewith.

5. The results seem to warrant the conclusion that extrapollen hypersensitivity may be given as a factor, which when present to a marked degree, precludes the possibility for complete and successful desensitization in seasonal hay fever treatment. It is, therefore, urged that all seasonal hay fever subjects be tested *routinely* with the inhalant and food proteins.

6. No connection was found to exist between the type of sensitization and the percentage of eosinophiles in the blood. This is in accord with Brown.[9]

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AN INDIRECT METHOD OF TESTING FOR CONDITIONS OF ATOPIC HYPERSENSITIVENESS

Second Preliminary Report*†

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A TECHNIC for an indirect method of testing in conditions of atopic hypersensitiveness, employing as its basis the principle of transferred local specific hypersensitiveness, as demonstrated by Prausnitz and Küstner,[1] was presented in a preliminary report by S. D. Kramer and myself.[2] Further studies in a series which now totals 95 cases more firmly establishes the feasibility of this technic as an aid to diagnosis in selected cases where direct testing of the patient is impossible, inadvisable, or impractical. The series includes: cases of acute and chronic atopic eczema in children and adults, with and without secondary infections; patients with abnormal skins (ichthyosis, urticaria, etc.); patients with abnormally reacting skins (marked dermographism); asthmatics constantly under the influence of adrenalin; infants and children with clinical histories of extreme degrees of sensitivity; patients who for various reasons possess a marked aversion to direct testing; infants and very small children whose parents were opposed to any form of direct tests on the child; patients on whom direct testing resulted in numerous positive reactions, the specific atopic nature of which had been questioned; and other cases of similar type.

The original technic of indirect testing has been repeatedly altered in an attempt to overcome some of the difficulties which a wide application of the procedure disclosed. The last form employed may be described as follows: from 5 to 10 c.c. of the patient's blood are obtained by venous puncture, under sterile precautions, at the elbow or external jugular vein. Dry syringes are used to avoid hemolysis. The blood is defibrinated at once by whipping and then centrifuged. The serum is drawn off and sterilized by Berkefeld or Seitz filtration. It is then kept in a tightly stoppered tube in the ice box.

As a "substitute," a nonatopic individual is preferable, since atopic individuals, as a group, are less receptive to passive local sensitization than normals.[3] During the period of sensitization and testing, fish, eggs, and nuts are omitted from the substitute's diet, as these foods

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following their ingestion are prone to induce wheal formation at sites sensitized to these substances.[4] Passive local sensitization is accomplished by injecting the subject intradermally with 2 rows of 7 or 8 sites about 3 or 4 cm. apart on the external aspect of each arm. The sites are outlined with ink. The forearms have been abandoned as a site for indirect testing, as wheal formation is less pronounced here than on the upper arm.[5, 6]

Testing the sites is delayed from forty-eight to ninety-six hours in order to permit all signs of the sensitizing injection to disappear, and all refractoriness resulting from the original wheal to wear off.[3, 7] Testing is contraindicated in the presence of erythema or any signs of inflammation.

The test consists of an intradermal injection of about 0.02 c.c. of atopen solution into the sensitized site. It is controlled by a similar test on normal skin about 5 to 7 cm. to the side of the sensitized site. The dilution of the atopen is the same as that used ordinarily for intradermal tests and may be varied according to the same indications which govern the concentration of testing solutions in direct testing. Alternate sites are used on each day so that neighboring reactions do not merge.

The simultaneous presence of too many positive reactions will induce a constitutional reaction in the substitute[2] in which all sensitized sites tested and untested will light up in a localized urticaria. This induces refractoriness of the site and hampers further testing. To prevent such constitutional reactions, it is advisable to await the results of tests on half of the sites before proceeding to complete the remainder. Usually 14 or 16 sites are tested on the first day, the others on the second. Some sites may be used a second time for testing with other atopens. A site should not be retested before a lapse of from forty-eight to ninety-six hours, in order that all signs of inflammation and refractoriness resulting from the original test be allowed to subside. It is not advisable to use for further tests any site that has once been the seat of a moderate or marked reaction, because of its refractoriness. Second tests on a site should always be made with atopens biologically unrelated to that used in the first test. Whenever possible, controls for such tests should be inserted into the same sites as the controls for the original test.

Diagrammatic records of the reactions must be kept, in order that subsequent retesting of a site may be governed by the nature and result of the first test.

The reactions are read a little later than in the direct method to allow the initial erythema due to skin trauma to subside. The test and control are read together. The size of the wheal, the amount and intensity of erythema, and the presence of pruritis are recorded for each. The interpretation of the reaction depends, not upon its size,

but upon the comparison of the reaction upon the sensitized site with its control. *Any excess* of reaction of the sensitized site over the control, no matter how minute, *either* in erythema, *or* wheal, or both, may be considered a positive reaction. When these factors are alike on both sites, the reaction must be considered negative regardless of size. When the wheal or erythema of the control exceeds those on the test site, the latter may be considered refractory and the test should be discarded. When the control is more than a slight reaction, the test should not be trusted. Pruritis is a confirmatory symptom to the positiveness of a reaction, but it should not be considered a reliable criterion without the objective evidence of erythema or wheal excess. Confirmation of doubtful reactions on new sites or by direct testing of the patient is advisable. "Splash" effects due to air bubbles in the syringe are to be guarded against as in direct testing.

Any positive reaction which can be consistently elicited indicates the presence of reagins in the patient's serum for that atopen. The size of the reaction does not measure the clinical significance of the atopen, nor is it wise to judge the relative importance of atopens by a comparison of the size of these reactions on sensitized sites.

The advantages of the indirect method of testing are: (1) tests are performed on normal skin; (2) the subject taking the test is an adult; (3) every skin test can be perfectly controlled; (4) testing is usually completed within seven to ten days; (5) the danger of constitutional reaction in the patient is avoided. The disadvantages of the procedure are: (1) there is a possibility of failure in transferring sensitivity to the subject; (2) the highly specialized technic permits its employment only by the specialist.

Any comparison of the indirect method with the direct on the basis of percentages of positive reactions obtained with each is untrustworthy, for some of the positive reactions elicited by the direct method (for example the reactions of Du Bois, Schloss, and Anderson[8] and those following the administration of horse serum) are not based upon a reagin mechanism.[3, 9] Information as to the frequency of failure to transfer passive local sensitivity is being determined by studies with sera of cases demonstrating positive skin reactions of which the significance has been definitely corroborated clinically. Regardless of the possibility of failures of transferring sensitivity in the indirect method of testing, it must be remembered that this procedure is usually employed in those cases where direct testing is impossible or impractical, and under such circumstances no other choice in technic is available. The employment of the indirect method in the present series has been in many cases so gratifying—the more so because in many instances a diagnosis by direct testing was an impossibility—that its further study and development are warmly recommended.

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SIMILARITIES AND DIFFERENCES IN BACTERIAL AND NONBACTERIAL ALLERGY

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THERE is much confusion connected with the subject of allergy which can be clarified only by accurate observation and frank discussion.

Wherever we find nonbacterial allergic phenomena producing disease, we are to assume that the reaction is the answer of the tissues to an insult produced by some substance which, having entered the tissues through some abnormal route, and having escaped the body's normal action by which it is prepared for assimilation, finds itself a foreign substance, in intimate connection with the body cells and disturbing their physicochemical properties. That the occurrence of this reaction in some individuals and not in others may depend upon a particular property of the tissues, a certain physicochemical background, seems more than a possibility.

Wherever we find allergic phenomena in the course of bacterial disease, we must assume that the reaction is due to some substance or substances produced during the growth of the causative microorganisms or derived from their destroyed bodies, which has come in intimate contact with the patient's cells after they have been acted upon and sensitized by a previous identical infection. The result of this contact is an inflammatory response.

While allergy is a phenomenon connected with many diseases, such as tuberculosis, streptococcal infection, undulant fever, and typhoid, it is probably best known in tuberculosis, the phenomena connected with it having been observed and described by Koch in 1891,[1] but not named until after the studies of von Pirquet[2] in 1907, which resulted in discovering the allergic phenomena in the skin of those who were infected by the tubercle bacillus.

Tubercle bacilli, on entering the body for the first time, irritate the local cells which answer the insult by the formation of tubercle, which is an attempt on the part of the body to localize them. This is a nonspecific and largely a noninflammatory defensive effort. It has recently been shown that the protein fraction of the bacillus has no part in the stimulation of epithelioid cells and tubercle formation, but that this belongs to the lipoid fraction of the bacillus (Auclair and Paris,[3] Sabin[4, 5] and Anderson[6, 7]). So far as we know there is no similar epithelioid cell defense against nonbacterial allergens. Both bacterial and nonbacterial protein, however, as well as certain other allergens,

cause a hypersensitivity of the body cells, which causes them to react allergically whenever they come again in contact with the same substances. Before allergic phenomena can stand on a secure scientific footing, and before the clinical allergic problems can be satisfactorily explained, it will be necessary to understand in what manner this cellular allergic response of the body to these two classes of substances corresponds and in what way it differs; and the reason for this similarity and difference.

There is some doubt as to the specific nature of nonbacterial allergy and as to its being more than an accidental part of the disease. We find patients sensitized to so many substances at times that it seems far more rational to assume that we are dealing with an underlying cellular state on the part of the individual which permits of an unnatural entrance of allergens, in general, into the body, and which requires an unnatural reaction to them when they have once entered, rather than with a condition which is brought about by a definite substance. Yet when an individual is found to be sensitized to several substances, more than one reagin can be demonstrated in the blood (Coca[8]). In bacterial allergy, on the other hand, the reaction does not occur simply because of the fact that bacteria find themselves in the tissues, but because the body cells have been sensitized by the action of certain substances produced and released during the growth and destruction of microorganisms responsible for a previous identical infection.

RELATION OF ALLERGY TO IMMUNITY

That allergy, as we describe it, takes part in the specific defense of the organism against a variety of substances, both bacterial and nonbacterial, is definite; but just what this part is, is the question. In tuberculosis, after the body cells have once been sensitized by previous infection with tubercle bacilli, allergy of varying degree, from a slight hyperemia to a severe exudation, even to necrosis of tissue, may be met whenever reinoculations of bacilli or bacillary protein take place; the degree of allergy depending on the dosage and virulence of the bacilli and the reacting capacity of the host (Krause[9, 10] and Pottenger[11, 12, 13]). Such allergy is a specifically acquired reaction and is usually considered as a part of the host's protective mechanism. The relationship as usually accepted has recently been questioned by Rich.[14] It seems definite that allergy is not coextensive with immunity, and if we may use the experience gained by the study of nonbacterial allergy and also ideas suggested in our studies of the phenomena as met in bacterial disease, we might be justified in assuming that it is a protective mechanism which is rendered unnecessary when immunity has been attained; for, if the host were in a state of absolute immunity, it is probable that he would also be in a state of desensitization.

Allergy, then, should be looked upon as an increased alertness of the cells toward bacilli and bacillary protein developed as a part of specific resistance but only necessary until such a time as immunity can be established. When immunity has been established, however, the host no longer finds it necessary to react violently with inflammation when bacilli attempt an implantation, for the tissues are uncongenial to bacillary habitation the same as we find them after infections which produce, as a rule, only one disease episode in man, such as measles, whooping cough, and smallpox. Individuals who have been rendered immune to the microorganisms which produce these diseases by one infection are often exposed to them again during life, but disease rarely appears a second time.

A condition of absolute resistance to reinfection with tubercle bacilli is never supposed to be attained in man; yet we do have instances reported in which patients who have recovered from tuberculosis, later failed to show skin reactions to cutaneous and intracutaneous tests of tuberculin. Krause reports such a case which he kept under observation for several years. I have seen patients who failed to react to the usual test dose of tuberculin years after treatment, although they had previously harbored lesions of sufficient magnitude to cause clinical symptoms. Whether they would have reacted to still larger doses had they been given, of course, was not proved. Certain clinicians have insisted that the way to use tuberculin to the best advantage of the patient is to use very large doses, and repeat and increase them until they no longer cause reactions on the part of the patient. Rich[14] believes the desensitizing effect of tuberculin by which the patient becomes better able to withstand his own tuberculoprotein is an important factor in tuberculin therapy.

The idea of there being a difference between allergy and immunity is in line with the clinical observation that, as tuberculosis advances and becomes chronic, the degree of allergic inflammatory reaction seems to grow less severe, not only relatively, but, actually, in proportion to the size of the reinoculations of bacillary protein which take place. We cannot, by any process of reasoning, assume that the numbers of bacilli or the amount of tuberculoprotein gaining access to new tissues and the blood stream are less in these far advanced lesions, where very extensive areas of disease are present, than in the limited ones of the early periods of the disease. On the contrary, it is reasonable to assume that the quantities are multiplied many fold. Therefore, we must assume as an alternative that the cells are less sensitive and that consequently they fail to show a degree of allergic inflammatory response corresponding to that which characterized their earlier contact with bacillary protein. Desensitization of the body cells to tuberculoprotein thus becomes an important part of specific defense and a necessary accompaniment of advancing disease.[15]

Again, the probable truth of the assumption of a relatively greater hypersensitivity of cells in early tuberculosis than in late tuberculosis is shown in the difference between early and late cavity formation. Cavity often forms promptly when relatively large numbers of bacilli and relatively large amounts of bacillary protein are present in the tissues during the early days of clinical tuberculosis; but later, when with what seem, so far as we are able to judge, to be equal reinoculations, are met by even a reduced exudative inflammatory response, and not by a destructive caseating process. To account for this we must assume either that equally large reinoculations do not occur, which, on the face of it, is untenable, or that the host's reaction toward them has diminished or changed; for, after an early cavity has formed, patients may go through months of active tuberculosis with the disease steadily advancing, and yet escape further tissue destruction of a magnitude such as is represented by the first cavity.

Evidence that immunity may be established without cell sensitization and allergic reaction is furnished by the experimental work of Swift[16] in nonhemolytic streptococci; and by that of Mackenzie[17, 18] on pneumococci. Swift found that by intravenous injection he was able to create a high degree of resistance without producing skin sensitiveness, while in the intracutaneously and subcutaneously injected animals, skin sensitiveness accompanied the increased resistance.

In tuberculosis it seems perfectly reasonable to assume that while cell sensitization and the allergic reaction are necessary for defending the patient against the spread of bacilli during certain phases of the disease, immunity is a further accomplishment and probably such a state of the body cells that protection against the specific microorganism no longer requires such explosive reactions as those represented by the acute inflammatory phenomena of active allergy.

The desensitization which is practiced in the treatment of so-called allergic diseases has for its purpose the changing of the state of the cells so that they are no longer sensitive to the causative substance, or changing the condition of the patient so he will no longer need to combat these substances by sensitized cells and the consequent allergic phenomena. Desensitization to the reinoculations of tuberculoprotein, which occur so frequently during an extending tuberculous process, is doubtless a similar accomplishment. Its artificial production has long been recognized by clinicians as being one of the principal aims of the therapeutic use of tuberculin.

BACTERIA AND NONBACTERIAL SUBSTANCES WHICH PRODUCE ALLERGY GAIN ACCESS TO TISSUES IN DIFFERENT MANNER

There is a difference in the manner in which bacteria and nonbacterial substances gain access to the tissues.

There is a hereditary element back of so-called allergic disease (Pot-

tenger[19] and Hurst[20]). Patients who suffer from asthma, hay fever, and urticaria give a history of the same condition being present in forebears in about 50 per cent of instances and the same is transmitted to future generations, as shown by the history analysis by Spain and Cooke[21] and by Ratner and Gruehl.[22] They seem to inherit a tissue which is more permeable than normal. Constitutionalists speak of them as belonging to the exudative and arthritic diatheses and as possessing cells which on account of their permeability allow the passage of foreign protein with greater facility than those whose cells are less permeable (Bauer[23] and Pende[24]). This is supposed to be at least one factor which is responsible for certain persons becoming asthmatic or suffering from hay fever, urticaria, or other forms of allergic reaction, while others do not. The cells of susceptible persons fail to interpose an effective barrier against such substances as pollens, foods, and animal substances. Entering the body through abnormal routes, they are attacked by the body forces in an abnormal way, and in their destruction a mechanism is set up which is applicable to future reaction against the same or similar substances; so that on reentry these substances are met by cells which are hypersensitized to them and are prepared to attack them. The result is an allergic response. The more highly sensitized the cells are, the greater their reaction. Orteil[25] has recently been able to show a different body chemistry in those suffering from so-called allergic diseases, indicating a different physicochemical tissue composition.

Sensitization to allergens is a property which may be possessed by all cells of the body, but it affects different cells to a different degree. Consequently allergic reactions in different tissues differ. This is evident in the location of different allergic diseases. It is also shown in the variation of skin tests on different portions of the body surface of the same individual when given simultaneously.

In tuberculosis, heredity seems to play no such part in *infection* as it does in the entrance of nonbacterial allergens to the body, for infection has long been recognized as being all but universal in the human family (Hamburger[26]) and still is, according to Opie and his coworkers,[27, 28, 29] at least in the city population. On the other hand, heredity plays a very important rôle in the patient's resistance to the *spread* of infection after bacilli have once gained entrance to the tissues. There may be something in the character of the tissues; in fact, I am inclined to think there is, which makes certain individuals who harbor a primary infection within their bodies more prone to break down with tuberculous disease than others who harbor what seems to be a similar infection.

Whenever tubercle bacilli or bacillary protein escape from an existing focus into new tissues, or reenter the body from without, allergy manifests itself within a few hours. It has been determined experi-

mentally that this occurs in from four to forty-eight hours. In nonbacterial allergy the reaction comes on much more quickly. I have seen a major attack of hay fever precipitated within a fraction of a minute on a sensitive child putting a daisy to its nose.

The tissues of one already infected with tuberculosis manifest resistance to further entrance of bacilli. In fact, while a few bacilli will inoculate the noninfected, and pass through the tissues with great rapidity; when a person suffers from advanced tuberculosis, countless numbers of bacilli may pass over the mucous membranes of his bronchi daily without producing local lesions; and, we assume, without producing infection at all in most instances, because the patient may go on to a recovery regardless of their presence in large numbers.

From these two examples we see that there is apparently a fundamental difference in the behavior of the sensitized body cells toward the entrance of bacteria (tubercle bacilli), on the one hand, and of nonbacterial substances, on the other hand. The former are prevented from entering or hindered in their entrance, while the latter are apparently aided. This, however, may be only apparent. Possibly we are thinking of conditions as similar which are very different. Possibly minute quantities of nonbacterial allergen contact local cells of higher sensitization, while the tubercle bacilli contact cells of lower sensitization.

DIFFERENCE IN REACTION OF THE BODY TO BACTERIAL AND TO NONBACTERIAL SUBSTANCES

There are differences in the allergic reactions produced by bacterial products as observed in tuberculosis and in that produced by nonbacterial substances, as seen in so-called allergic diseases which may be set forth with advantage to our discussion. These manifest themselves in quickness of response, character of response, and persistence of response.

As previously stated, the reaction of the allergic diseases may come on very quickly, after contact with certain allergens, while that in tuberculosis is much slower in developing. Zinsser[30, 31] and Enders[32] have shown that there are two distinct fractions in tuberculin, one of which acts like other coagulable proteins and quickly produces cell-sensitization and anaphylaxis; the other, a noncoagulable protein which also sensitizes cells but produces a slower allergic reaction. This latter they consider as being connected with the immunity mechanism. We undoubtedly are discussing two somewhat related yet different phenomena in bacterial and nonbacterial allergy. Progress demands that these two reactions be compared and contrasted until they are understood. Difference in nomenclature in the two reactions would probably facilitate their study.

The character of the response to bacterial and to nonbacterial aller-

gens, both local and general, is vastly different. In nonbacterial sensitization the local blood vessels dilate rapidly, their walls become permeable, and an exudation quickly takes place. There is little or no tendency to destruction of tissue or formation of new tissue. In asthma and hay fever the mucous membranes become so edematous that the air passages are markedly encroached upon, yet all will disappear in a short time if the attacks are relieved. It is only when the condition becomes chronic that structural changes occur (Huber and Koessler[33] and Hansel[34]). The reaction in tuberculosis, in contrast to this, is particularly marked in the tissues with which the bacilli or escaping undiluted tuberculoprotein come in contact; and less marked in other tissues which are the seat of unhealed tuberculous infection and which contact the tuberculoprotein in a very dilute form after it has been diluted by the entire volume of blood; and still less in other cells of the body (Pottenger[11, 35, 36, 37]). Tuberculo-allergy is likewise accompanied by an exudation, either mild or severe; but one which persists, often for weeks and months. In tuberculosis, too, the allergic reaction leads to two opposite phenomena—the destruction of tissue and the formation of new tissue; while neither of these pathologic processes becomes a prominent part in acute nonbacterial allergy, although structural changes follow chronic manifestation.

These two types of allergic reaction are accompanied by a very different general reaction, which is expressed in different components of the vegetative neurocellular mechanism. The general symptoms which accompany the body's reaction to nonbacterial protein are expressed in a vagus (parasympathetic) syndrome (Pottenger[38, 39, 40]), as is illustrated in asthma, which consists of a bronchial spasm, increased secretion of the secretory glands in the bronchial mucous membrane, increased permeability of blood vessels and local cells, an increase in the normal potassium-calcium ratio (Kylin[41]), an increase in alkalinity of tissues, and an eosinophilia. That belonging to other so-called allergic diseases, such as hay fever, urticaria, and angioneurotic edema, is similar, differing though in the location of the reaction.

A genuine toxic syndrome can be brought about by nonbacterial protein when employed in certain ways but this is not the usual syndrome shown in the allergic diseases.

The general symptoms of allergy met in tuberculosis, on the other hand, are expressed in the sympathetic system (Pottenger[40, 42, 43]). It may or may not be accompanied by an increase in the body temperature. If the reaction is severe, it is met by evidence of widespread stimulation of the sympathetics, thus: chill, fever, contraction of the pilomotor muscles, sweating, rapid heart, poor appetite, diminished digestive ability, constipation, malaise, leucocytosis, a decrease in alkalinity of the blood, and anemia. When the allergy is mild, the acute toxic syndrome is absent but some of the symptoms of sympathetic

stimulation, such as sweating; rapid heart; malaise; poor appetite; and slow digestion, particularly on exercise; and leucocytosis are present.

There is also a wide difference in the persistence in reaction in these two types of allergy.

Nonbacterial allergy may disappear as by magic, as is so often seen following the administration of adrenalin in an acute attack of asthma or urticaria. Atropine, because of its inhibitory action upon the parasympathetic system, will also combat some of these phenomena, but cannot be given in doses sufficiently large to be effective without at the same time making the patient very uncomfortable. Calcium will strengthen the action of the sympathetics (Pottenger[40, 44, 45]), aid in restoring the calcium-potassium balance, and lessen the permeability of the cells (Lilly,[46, 47] Zondek,[48] and Pottenger[39, 40]). In patients in whom a deficiency of thyroid is suspected, thyroid preparations may be administered for their effect on the sympathetic nerves and for the purpose of mobilizing bone calcium so that it may be utilized by the body, as shown by Aub.[49, 50] Lastly, the toxic syndrome relieves asthma. Asthmatic patients may be relieved by acute temperature reactions, by which the sympathetics are stimulated and adrenalin increased, and the preponderant parasympathetic action in the bronchi is opposed (Pottenger[40]).

Allergic reactions in tuberculosis are slow to disappear. If they are accompanied by marked exudation in the tissues, weeks and often months are necessary for these to disappear; and, if followed by loss of tissue, months and years may be required, or they may never be restored. It may be that the reason why these allergic phenomena do not disappear more quickly is because they are kept up by frequently repeated reinoculations, for the depot of supply is present so long as active infection is present. There is no way of knowing the exact part that this factor of reinoculation plays; but such a thing as the magical disappearance of the exudation and bronchial spasm which may be brought about in asthma by the employment of adrenalin has no parallel in the clearing up of the phenomena of tuberculosis. Our method of attack in tuberculosis is to employ such measures as will limit reinoculations and build up the patient's physical strength; and then rely on the patient's specific powers of defense, alone or assisted, to aid in the destruction, retardation of migration, and encapsulation of the bacilli; the desensitization to his own tuberculoprotein; and the clearing of the inflammatory field and restoration of injured tissue.

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THE POTTENGER SANATORIUM AND CLINIC.

HAY FEVER*†

A Sketch of Its Early History

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IT WAS Carlyle who expressed the view that history is the essence of innumerable biographies and that anyone who wishes to know the history of any period or of any country must know the men who made it what it was. Medical history, on the other hand, is concerned more with ideas than with biography. The latter is of value only in so far as it bears on ideas. One must concede, however, that some knowledge of the life and achievements of a physician who has made some important contribution to medical science does frequently add a human quality to the idea which the latter would not possess without this knowledge.

The hundred years from the first quarter of the nineteenth century to our own time encompass the historical development of our present knowledge of hay fever. The recognition of the disease as a clinical entity, the presentation of experimental proof of its pollen etiology and the development of methods for its prevention and control have all been achieved during this period. Many of the physicians who contributed to this important knowledge were themselves sufferers of the malady. It is with these early observers and the significance of their observations that it is my purpose to deal in this historical sketch.

Author of the First Clinical Description of Hay Fever

On March 16, 1819, Dr. John Bostock (1773-1846), an English physiologist and clinician, read a paper before the Royal Medical and Chirurgical Society of London on a *Case of a Periodical Affection of the Eyes and Chest*,[1] in which he presented to the members the history and clinical symptoms of a seasonal affection which had troubled him since childhood. Nine years later[2] he gave a more detailed account of the disease, applying to it the noncommital name of "catarrhus aestivus" or summer catarrh, although the affection had, since his earlier publication, obtained the popular name of "hay fever."

The recognition of hay fever as a clinical entity dates from Bostock's description of his own symptoms, a fact which has been recognized by the German school in giving to hay fever the designation Bostock's catarrh. Even though Bostock's achievement is somewhat dimmed by his failure to discern that pollen was the cause of the disease, the credit for its first clinical recognition justly belongs to him.

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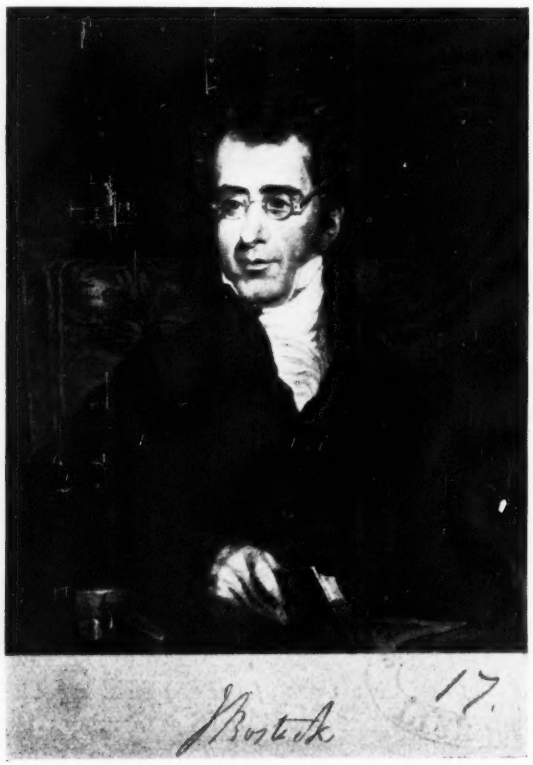
It is very doubtful whether certain forms of seasonal catarrh described by medical writers in the sixteenth, seventeenth, and eighteenth centuries were instances of hay fever. The cases of Botallus of Pavia (1565), and Binningerus (1673) are often referred to in the literature in support of the view that hay fever was first described several hundred years before Bostock. The former tells of patients who had an intense aversion to roses, since their odor caused them headache, itching of the nose and sneezing, and the latter reports the case of a lady



who every year for a period of several weeks had symptoms of coryza when the roses bloomed.[3] Although it is highly probable that hay fever had occurred long prior to the time when it was first noticed by medical writers, it appears to have been mistaken for a mere modification of the summer catarrh. This is not remarkable when one reflects that up to the time of Sydenham, in the seventeenth century, rheumatism and gout had been regarded as one and the same disorder and that these diseases have less similarity and are more distinct in their characteristics than are hay fever and common coryza.

Bostock who was somewhat of a medical historian himself states in his paper: "One of the most remarkable circumstances respecting this complaint is its not having been noticed as a specific affection, until

within the last ten or twelve years. Except a single observation of Heberden's, I have not met with anything that can be supposed to refer to it in any author, ancient or modern." The observation of Heberden to which Bostock refers is to be found in his Commentaries, that great mine of keen medical observation which was the result of a lifetime of conscientious note-taking.[4] Speaking of this form of catarrh, Heberden states: "I have known it to return in four or five persons annually in the months of April, May, June, or July and last a month with great violence."

CASE

OF A

PERIODICAL AFFECTION

OF THE

EYES AND CHEST.

BY JOHN BOSTOCK, M.D. F.R.S. & L.S.

Read March 16, 1819.

THE following case, it is presumed, will not be altogether uninteresting to the Society, as affording an example of an unusual train of symptoms, and it may perhaps be considered the more worthy of their attention, from its having occurred in the person of the narrator.

J. B. æt. 46, is of a spare and rather delicate habit, but capable of considerable exertion, and has no hereditary or constitutional affection, except various stomach complaints, probably connected with, or depending upon, a tendency to gout. About the beginning or middle of June in every year the following symptoms make their appearance, with a greater or less degree of violence.

Although the name of John Bostock will be remembered for his clinical description of hay fever, it is for his contributions to physiology and physiologic chemistry that he was held in high esteem during his lifetime. Pettigrew[5] in his *Biographical Memoirs* has given an excellent narrative of the life and work of John Bostock. Born in Liverpool in 1773, Bostock followed in the footsteps of his father, a practicing physician in that city. In his twentieth year he commenced the study of medicine by spending some time with an apothecary, in order to become familiar with pharmacy, and afterward as attending physician to the Liverpool General Dispensary. After several years devoted to the study of anatomy in London and of chemistry in Edinburgh, he took his medical degree at the latter University in 1798, when twenty-five years old. His thesis on this occasion was upon secretion.

On leaving Edinburgh, Bostock settled in his native town and was elected one of the physicians to the Liverpool General Dispensary. It would appear, however, that he devoted more time to the study of botany, physiology, and chemistry and to the writing of many papers for various medical and scientific journals than he gave to practice. In fact, in 1817 he gave up the practice of medicine and determined to devote his attention more particularly to the study of physiology. At the age of forty-four he moved from Liverpool to London. In making this change he was principally influenced by the greater facilities which the metropolis afforded for the pursuit of his chosen work and for the enjoyment of the society of his scientific friends.

The London group of physicians into whose circle Bostock now entered were among the most famous of the century. The Roster of the Royal Medical Chirurgical Society of that time contains such names as Jenner, Matthew Baillie, and the "great men of Guy's," Thomas Addison and Richard Bright. As one of the lecturers on chemistry at Guy's Hospital, Bostock doubtless came under the influence of Bright. Stimulated by the latter's work on nephritis, Bostock made chemical analyses of the urine and studied the urea content of the blood of patients with Bright's disease.

Bostock's most noteworthy contributions were made in physiology. His work entitled *An Elementary System of Physiology* published in London in 1823, passed through three editions and was the first systematic and connected view of modern physiology that had been published in England. This and his numerous researches on the chemistry of the body fluids show him to have been "characterized by a bold and ingenious spirit of inquiry."

GROPING AFTER THE CAUSE OF HAY FEVER

It is not unusual for certain fundamental medical facts to become rooted in the traditional beliefs of a people long before the tests of observation and experiment have proved them worthy of acceptance by the medical world. The annals of medical history abound in many examples. In Gloucestershire, the home of Jenner, for instance, it had long been a country-side tradition that dairymaids who had contracted cowpox through milking did not take smallpox, a fundamental concept in the prevention of the disease. It was the information imparted to Withering by an old grandmother near Birmingham that foxglove was good for dropsy that set him to work to try it in heart disease. Peruvian bark had been used by the Indians and Jesuits in malarial fever long before the discovery of its active alkaloid quinine.

The use of the popular name hay fever shows that the conception of the complaint as produced by hay fields or attributable to hothouses and to the aroma of flowering grasses prevailed at large during the first quarter of the nineteenth century. That Bostock did not share

this opinion is clear from his statement: "I think myself fully warranted in asserting that, in my own case, the effluvium from hay has no connection with the disease."[2] Bostock believed his symptoms due to exposure to rays of the sun.

William Gordon who was a contemporary of Bostock took a different view of the cause of hay fever. From the study of a patient suffering from hay asthma he concluded that the disease was caused by the "*aroma* emitted by flowers of the grasses," particularly from those of sweet vernal grass *(Anthoxanthum odoratum)*. In summing up his observations, Gordon states: "I have said that the *Anthoxanthum odoratum* seems to be the principal exciting cause of hay asthma, and I am induced to come to this conclusion, first, because this plant is one of the most scented of the grasses; and second, because as soon as it begins to flower and not until then, the asthma commences; as the flowers arrive at perfection the disease increases, and after they have died away I have remarked that patients could pass through the most luxuriant meadow with total immunity. The disease, then, should rather be denominated grass asthma than hay asthma, since hay seems incapable of producing it."[6]

John Elliotson (1786-1868), who was also a contemporary of Bostock, argues forcibly against the views entertained by the latter, and in his clinical lecture delivered at St. Thomas' Hospital on March 31, 1831, he makes the definite suggestion that hay fever depends on the flower of grass and probably upon the pollen. When his lecture on hay fever was delivered, Elliotson was at the height of his career as a teacher and consultant in London. His great industry, his acknowledged abilities, and his prepossessing manners made it possible for him to forge ahead in London. A year after his graduation from Cambridge in 1821 he was elected physician to St. Thomas' Hospital, where he became the most energetic teacher of the day, and largely responsible for the introduction of bedside teaching into the London hospitals. His clinical lectures, published in the *Lancet* in 1829 and subsequent years became models because of the concise and practical way in which they were presented. These able lectures did much to enhance Elliotson's growing reputation and according to his own statement his professional income rose in one year from five hundred pounds to five thousand pounds.[7]

It is, perhaps, not generally known that Elliotson was one of the first, if not the first, in England to advocate the use of the stethoscope introduced into practice by his French contemporary, Laennec, in 1819. His lectures on hay fever are of particular interest to the student of allergy because Elliotson was probably the first to mention the occurrence of a dermatitis of the hands following the handling of the flowers of grass. In referring to this observation he writes: "On han-

dling the flowers of grass, her hands always became instantly inflamed; therefore there is clearly in her skin a peculiar susceptibility of irritation from the flowers of grass''; and he concludes, ''I presume that the same morbid state exists in the mucous membranes of the air passages.''[8]

This keen observer also anticipated by a quarter of a century Hyde Salter's classical description of hay fever and asthma following expo-

sure to animal emanations. Of a woman patient sensitive to rabbit emanations, Elliotson writes that they ''produced a running at the nose and eyes and soreness of the upper lip, that if she went into a place where there were rabbits, it came on; and that if her husband came in after having shot a rabbit and threw it down near her, those effects were instantly produced.''[8]

Unfortunately the great error of Elliotson's life was the espousal of the cause of mesmerism. In 1843 he published a pamphlet describing

Numerous Cases of Surgical Operations Without Pain in the Mesmeric State. His wards became filled with hysterical and excitable girls who were magnetized to sleep in order to try the effects of the new remedy, the fame of which had spread far and wide. The clinical clerks and other pupils were occupied in "manipulating" or as some called it, "pawing" the patients to obtain mesmeric effects. Because of these activities Elliotson fell into disfavor and resigned from the hospital and from his professorship of the Principles and Practice of Physic at the London University. Elliotson died in 1868 in his eighty-second year.

The year 1859 is a memorable one in the early history of hay fever, for in that year Phoebus began the first monograph on the disease, Hyde Salter published his classical work describing cases of asthma and perennial hay fever due to animal emanations, and Blackley commenced his ingenious experimental researches on the pollen etiology of hay fever.

The monograph[9] of Phoebus (1804-1880), professor of medicine at the University of Giessen, and one of the foremost pharmacologists of his day, was published in 1862. This work brought together and put into available form all that was known of hay fever up to that time with a care and minuteness which is quite characteristic of the mode in which the German mind deals with obscure and little understood subjects. As a result of his survey of the various causes then supposed to produce hay fever, Phoebus was not inclined to accept any one agent as the sole cause of the disease. While recognizing the fact that the attacks occur most frequently during periods when the majority of the grasses are in bloom, Phoebus accepted the view of Bostock that "The first heat of the summer is a stronger cause than all the grass emanations put together."

The classical work of Hyde Salter (1823-1871) on asthma[8] first appeared in 1859. Being himself a sufferer from the disease, he early in his career turned his attention to disorders of the chest and began to collect material for a work on his own malady. Hyde Salter's monograph was generally recognized as the best authority upon the subject, rapidly passing into a second edition. It was first written in individual papers for the medical journals, each paper afterwards forming a chapter of the volume. Although the work is primarily concerned with asthma, containing a painfully accurate description of his own sufferings, it also described instances of what Salter designates as summer asthma or hay asthma.

Of particular interest to the student of allergy is Salter's classical description of hay fever and asthma following exposure to animal emanations. His description of "cat asthma," perhaps the first in the literature should be read by every student interested in the subject.

Of this form of asthma he writes: "The cause of this asthma is the proximity of a common domestic cat; the symptoms are very similar to those of hay fever, and, as in the case of hay fever, are occasioned by *some sudden influence inappreciable by the senses.* I cannot recollect at what time I first became subject to the cat asthma, but I believe the liability has existed from the earliest period of life. I believe some asthma would present itself if I were sitting by the fire and the cat sleeping on the hearth rug; but the effect is much greater when the cat is at a distance of one or two feet, or still closer; it is still further increased by the raising of the fur and moving and rubbing about, as is the habit of cats when they are pleased, also by stroking their fur, but most of all when they are in the lap, just under the face . . . . With respect to the symptoms, I have only to say they closely resemble those of hay fever, with only such difference as might be expected from the near proximity of the cause, from its defined and local nature, and also for the facility for its entire and immediate removal." Hyde Salter then mentions some symptoms resulting from the action of this "cat poison" on the skin and mucous membranes; "I have often known the eyes and lips most painfully affected by being touched by the fingers after handling a cat. . . . . The effect on the eye of rubbing it just after touching a cat is to produce a hot, stinging irritation of it, a profuse flow of tears and injection of the whole eye, a tender painful swelling of the caruncula, and intolerance of light . . . . The result on the lips is an enlargement of the whole lip, and sometimes a sort of lump or protuberance at the part principally affected, together with a feeling of heat and irritation . . . . The wound from a claw, whatever be its form, is always surrounded by a white, hard elevation or wheal, very much resembling the appearance consequent on the sting of a nettle . . . . The saliva of a cat is perfectly innocent, and a bite with the tooth in no way differs from ordinary wounds of the same character; *in a word, I believe the influence is, in its source, exclusively cutaneous.*" (Chapter X, page 236.)

The whole work abounds in keen clinical observation recorded in a vivid style and shows a remarkable command of language for which Hyde Salter was noted. Educated under the eye of a father, who was himself a busy physician, Salter matriculated at the University of London, where he took his medical degree in 1851. Besides his pursuit of anatomic and physiologic studies, he amassed a large clinical experience first as physician to the Carey-Street Dispensary and later as physician to Charing-Cross Hospital. His unusual gift in pencil drawing added to his eminence as a clinical teacher, and his literary and musical talents are stated by his contemporaries, by whom he was held in the highest esteem, to have been rarely seen in a busy practitioner of medicine.[11]

THE FIRST EXPERIMENTAL RESEARCHES ON HAY FEVER

In his monograph on hay fever, Phoebus described what is probably the earliest experiment carried out by a hay fever patient upon himself. This was done by W. P. Kirkman, a German physician. The latter tells us that a day or two before Christmas he noticed in his hothouse a single plant of *Anthoxanthum odoratum* (sweet vernal grass) loaded well with pollen. This, he thought, afforded a capital opportunity for experimenting with this particular grass, so he plucked it, rubbed the pollen with his hand and sniffed it up his nose. Almost immediately it brought on an attack of hay fever which lasted an hour.

It is, however to the credit of Charles Harrison Blackley, of Manchester, England, and to Morrill Wyman, of Cambridge, Massachusetts,

Dr. Philipp Phoebus.

but more particularly to the former, to have given the classical experimental proof that pollen is the cause of hay fever. In analytic observation and ingenuity in devising experiments, Blackley's work[12] first published in 1873, has no peer even in our own time.

Very little appears to be known of the personality and other activities of this Manchester physician, who year after year for some fifteen years painstakingly and with discomfort to himself carried out the well-conceived pollen experiments on himself. One gleams from reading his monograph and published notes[13] that the observations were made and recorded during the busy days of an active practice.

No obituary on Blackley was published. His name still appears in Churchill's *Medical Directory for 1900*, from which we learn that Blackley was elected to membership in the Royal College of Surgeons in 1858 and that he received a degree of Doctor of Medicine from the University of Brussels in 1874, this probably supplementing his degree

of Bachelor of Medicine. That his medical interests reached beyond his work on hay fever, one may infer from some of the other titles of his listed publications: *On Progressive Pernicious Anemia and Its Successful Treatment; Observations on the Progress and Tendency of Some of the Modern Methods of Scientific Research; On the Etiology of Cancer; The Influence of Idiosyncracy in Determining the Susceptibility to the Action of Drugs; On the Symptoms of Lead Poisoning.*

Of his own case and the circumstances which lead up to his investigations on hay fever, Blackley writes, "I have, as I have previously said, suffered from hay fever for more than twenty-five years, but the exact time at which the disorder first commenced I cannot now remember. The attacks at first lasted only a few days, and then declined rapidly; and they seemed then to me, to be in some way dependent upon the commencement of warm weather." In discussing further the possible relationship of heat to the production of his symptoms Blackley says: "Another circumstance, which occurred in 1859, helped still further to cause me to doubt whether heat had any direct influence in producing the symptoms in my own case. A bunch of one of the grasses (I think it was the *Poa Nemoralis*) had been gathered by one of my children and placed in a vase in one of the rooms at home which I seldom entered. I happened, however, to notice the vase in going into the room a few days after the grass had been placed there, and on disturbing it to examine it, a small cloud of pollen was detached and came in close proximity to my face. I commenced sneezing violently in the course of two or three minutes, and had what I considered a rather smart, though short, attack of my usual summer disorder. As this grass flowers much earlier than the majority of the grasses cultivated for hay-making, and as there was little or no grass in flower in the meadows at the time, I was satisfied that the symptoms were due to the pollen which had escaped accidentally during the examination. From this time my investigations commenced and these have been carried on up to the present time as opportunity has offered."[14]

The exact analytic observations of Blackley and the accuracy of his deductions from them are indeed remarkable when viewed in the light of our present knowledge of hay fever. Being subject to the disease, Blackley tested on himself the pollen of nearly one hundred different species of grasses and flowers, in the fresh as well as in the dried state and also in some instances in the form of alcoholic extracts.

Five different ways of testing the pollen were tried: "1, by applying it to the mucous membranes of the nares; 2, by inhaling it, and thus bringing it into contact with the mucous membrane of the larynx, trachea, and bronchial tubes; 3, by applying a decoction of the pollen to the conjunctiva; 4, by applying the fresh pollen to the tongue, lips, and fauces; 5, by inoculating the upper and lower limbs with the fresh

moistened pollen." (Chapter XIV, page 96.) Blackley found that the pollen of rye caused more violent symptoms than that of the grasses, whereas the pollen of wheat and oats had about the same activity as that of the grasses. He states, however, that "the action of the pollen of the order *Graminaceae* was on the whole very distinct and well marked, and that so small an amount as $\frac{1}{200}$ grain of pollen applied to the nasal mucous membrane produced hay fever symptoms." The inhalation of the pollen of certain plants and grasses produced asthmatic attacks and constitutional symptoms.

Blackley was probably the first to perform the skin test with pollen. Of this experiment he writes: "Whilst I was still suffering from my usual attack of hay fever, during the summer of 1865, as much pollen as could be obtained from two antlers of the *Lolium italicum* was applied to the center of the anterior surface of the forearm after the skin had been abraded, and to this the quantity of pollen named was applied after being placed on a piece of wet lint the size of the abrasion. This was covered with a piece of gutta percha, and the whole was held in position by a strip of adhesive plaster. The center of the other forearm was treated in exactly the same manner save and except that no pollen was applied to it. The scratching with the lancet raised a wheal such as is seen in urticaria or in the stinging with nettles. In a few minutes after the pollen had been applied the abraded spot began to itch intensely; the parts immediately around the abrasion began to swell, but this was not apparently due to any action on the cutis vera. In the above experiment the swelling seemed to be entirely due to effusion into the subcutaneous cellular tissue" . . . . "The swelling attained its maximum in six hours, and then remained stationary for another eight hours; after this it gradually subsided, and in forty-eight hours it had entirely disappeared. The arm to which no pollen had been applied did not exhibit any sign of swelling or irritation." (Chapter XIV, page 104.)

Having established the fact that seasonal hay fever is caused by the pollen of plants, Blackley undertook a series of experiments to find out the quantity of pollen that might be floating in the atmosphere at low and high altitudes and the relationship between this quantity and the intensity of his own symptoms. The method which Blackley employed was essentially the same one used by workers today in studies of the pollen content of the air. After much experimenting on different methods, he decided on this simple procedure. Of this technic Blackley writes: "Ultimately I was led to adopt a very simple plan, which I afterwards found was recommended by Dr. Phoebus. This consists in the exposure of slips of glass to the open air for a given length of time, so as to allow any solid matter the air may contain to deposit upon the glass. Each slip of glass had a cell formed upon it with black varnish, so as to enclose a space one centimeter square. This square was coated with

a thin layer of fluid prepared for the purpose. (In a footnote he states that this fluid is made by mixing one part of water, two of proof spirit, and one part of glycerin.) After being exposed for twenty-four hours, each slip was placed under the microscope, and any deposit it contained was carefully examined, and the number of pollen grains counted." (Chapter XIV, page 150.)

The first series of experiments was made in meadow land about four miles to the southwest of the city of Manchester. Pollen was found constantly on the slides, and in large amounts during the whole of the hay fever season, varying somewhat according to the temperature and rainfall. He observed that fully 95 per cent of all the pollen collected on his glass slips belonged to the *Graminaceae*. In the city, Blackley found that there was on the average about one-tenth as much pollen as in the country. Inside his house if the windows were closed, he found very little pollen.

Experimenting between the months of May and August, 1866, he found that between May thirtieth and August first the quantity of pollen increased gradually up to the last week in June and then decreased. In his own case the hay fever symptoms increased and diminished as the amount of pollen in the atmosphere rose and fell. The pollenometric charts of today differ in no essentials from those made by Blackley in 1866, 1867, and 1869.

Other observations were made by attaching the glass slide to a kite, and thus examining the atmosphere at elevations of from 500 to 1500 feet. One of the observations is thus described: "The altitude attained varied, according to the force of the wind, from six hundred to eight hundred feet. The experiment occupied six hours. The wind blew all the time from the east, and consequently would pass over a large portion of the southern side of the city before it came in contact with the instruments. The nearest grass land would be from two and a half to three miles distant. Five hundred and eighty-four pollen grains were deposited in the upper slide in six hours." (Chapter XIV, page 176.)

In 1925, a half century after Blackley, the late Dr. William Scheppegrell, of New Orleans, confirmed Blackley's observations on the pollen content of the upper air strata by exposing pollen plates in an airplane at elevations of over ten thousand feet.[15]

The first noteworthy American contribution to our knowledge of hay fever was made by Morrill Wyman, of Cambridge, Massachusetts. With some other members of his family he had been a lifelong sufferer of an autumnal form of the disease. Besides Dr. J. A. Swett, of New York, who in his treatise on *Diseases of the Chest* published in 1852,[16] mentions a periodical catarrh occurring in the autumn, no physician had called attention to this form of the affection. In 1854 Wyman described the disease in his lectures at the Medical School of Harvard

University and in 1866 he read a paper on the late form of hay fever at the meeting of the Massachusetts Medical Society, giving it the name of "autumnal catarrh." His exhaustive monograph on *Autumnal Catarrh* (hay fever) published in 1872 is one of the best clinical analyses of the disease in our own medical literature. Wyman was one of the first to recognize in the pollen of ragweed (Roman wormwood, *Ambrosia artemisiaefolia*) one of the causative agents of autumnal hay fever. Of his experiments with ragweed, Wyman writes: "Early in September, 1870, I gathered in my grounds at Cambridge, Mass., some

DR. MORRILL WYMAN

Roman wormwood in full flower, covered with pollen, taking the whole plant, stalks and roots. This was carried to the White Mountain Glen, about 1200 feet above tide, where we remained till September 23 in the afternoon. The parcel containing it was then opened and freely sniffed by myself and son. We were both seized with sneezing and itching of nose, eyes and throat, with a limpid discharge. My nostrils were stuffed and my uvula swollen, without cough, but with the other usual symptoms of autumnal catarrh. These troubles continued through the night, and did not disappear till the afternoon following. Prof. Jef-

fries Wyman, who was of the same party, but did not sniff the plant, had none of the symptoms just described." (Chapter XVII, page 128.)

Similar experiments with ragweed were carried out on himself by Dr. Elias J. Marsh, of Paterson, New Jersey, in 1876 and reported in a paper read before the New Jersey State Medical Society in 1877. Marsh not only confirmed Wyman's observations but supplemented these with counts of the number of Ambrosia pollens in the atmosphere before and after the appearance of symptoms. In summing up his conclusions Marsh writes: "From these investigations the writer has formed the opinion that autumnal catarrh, like the English hay fever, is caused by the presence of the pollen of flowering plants in the atmosphere, and its irritant action on the respiratory mucous membrane of susceptible persons." (Chapter XVIII, page 100.)

The pollen etiology of hay fever, so ably established by the crucial experiments of Blackley and Wyman, was by no means generally accepted in Europe and the United States. Their work was published at the beginning of the bacteriologic era. Under the influence of the researches of Pasteur and Koch, hay fever began to be considered an infectious disease. Hermann von Hemholtz, who was a sufferer of the disease, described vibrio-like organisms which he considered the causative agents of hay fever. The bacterial theory of the disease found many adherents, although not one of Koch's postulates had been fulfilled in any of the experiments described.

In 1876 another monograph on hay fever appeared. This was written by Dr. George M. Beard, a neurologist of New York City.[19] Beard, who was well acquainted with the experimental researches of Blackley and Wyman, nevertheless concludes that the whole question of the origin and nature of hay fever is yet an open one and advances the view that the disease is primarily a neurosis.

More than a quarter of a century elapsed before Dunbar,[20] also a victim of the disease, repeated the main experiments of Blackley, elaborated them by new ones, and established beyond doubt the rôle of pollen as the cause of hay fever. Applying the modern methods of immunology to the problem, Dunbar and his pupils laid the scientific foundations which have made possible the evolution of methods for the specific diagnosis and treatment of hay fever during the past twenty-five years.

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A BOTANICAL SURVEY OF HAY FEVER-PRODUCING PLANTS IN THE PACIFIC NORTHWEST*

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ONE of the fundamental factors upon which the satisfactory results in the treatment of hay fever rests, is the thoroughness with which a locality has been investigated with reference to its wind-pollinated plant life.

Probably one of the most important developments in recent years that has given us an understanding of the factors that cause hay fever has been the collection of botanical data with regard to the wind-borne pollens in the various sections of the United States. The simple fact that a person who has severe symptoms of hay fever in one locality can sometimes move only a few miles and obtain complete relief, demonstrates that there must be a marked specific variation in the botanical make-up of individual districts. We can in many instances in this section of the country, get a good idea of the causative factors by having the patient tell us the season of the year in which his symptoms start and in which localities he has hay fever. A patient, for example, living in central Washington may have severe symptoms but as soon as he reaches the summit of the coast range and goes into Western Washington, will be completely relieved of his symptoms. A survey of these districts explains it quite simply since such weeds as Russian thistle and the sagebrushes do not exist along the coast.

Considerable data is now available regarding the botanical makeup of the more populated districts of the United States and have been ably reported by Scheppergrell,[1] Hall,[2] Watson,[3] Bernton,[4] Phillips,[5] Duke and Durham,[6] Kahn,[7] Balyeat,[8] Piness,[9] Rowe,[10] and Durham.[11] The Pacific Northwest has been noticeably neglected in such a survey and it is our pleasure to present an analysis of this portion of the country.

Five years ago, the botanical survey and collection of pollens in this locality was commenced by one of us (T. A. B.), and we are now able to report in detail upon the states of Washington, Oregon, Idaho, Montana, Colorado, Utah, and Wyoming. Because of the similarity of the flora in certain districts of the various states, it is necessary to subdivide the states into seven districts:

*Read before the Association for the Study of Allergy, at the Seventh Annual Meeting, Portland, Ore., July 8, 1929.

District No. 1 Western Washington and Oregon
" " 2 Eastern Washington and Oregon
" " 3 Southern Idaho, Western Wyoming and Utah
" " 4 Western Colorado
" " 5 Eastern Colorado, Eastern Wyoming and Eastern Montana
" " 6 Central Montana
" " 7 Western Montana and Northern Idaho

It will be noted that the distribution of certain plants follows certain life zones and by studying these zones, we can quite readily anticipate the types of flora that can be expected to exist in a certain locality. Upon this, one can explain the reason that Russian thistle occurs only in the eastern portion of Washington and not on the coast, or the occurrence of this same weed in a semi-isolated, intermountain portion of Western Montana.

District No. 1 includes that portion of Washington and Oregon that lies west of the Cascade range of mountains. In this district there are but two seasons. An early season that commences during February and at which time California hazelnut (Corylus californica), alder (Alnus tenuifolia), and the oaks (Quercus garryanna) pollinate and are considered the chief offenders. Their pollination season is of short duration and the number of hay fever cases are relatively small. The second season commences during April and continues until October. During this season the largest number of cases occur (about 90 per cent). Probably the greatest single factor occurring during this season is velvet grass (Notholcus lanatus) which is not only very abundant but produces an enormous amount of pollen during its pollination season. Timothy (Phleum pratense), orchard grass (Dactylis glomerata), perennial rye grass (Lolium perenne), Italian rye grass (Lolium multiflorum), Kentucky blue grass (Poa pratensis) and the brome grasses (Bromus inermis, hordeaceous, secalinus) also are common offenders. English plantain (Plantago lanceolata) is quite abundant in this district and it has been proved a definite factor. Its pollination season is comparatively long, commencing during May and continuing into October and probably is responsible for causing symptoms extending into October.

District No. 2 includes that portion of the states of Oregon and Washington lying east of the Cascade range of mountains and limited on the east by the Rocky Mountains. Here are three distinct seasons. The first commencing during February is of short duration since the trees are the factors, notably the birches (Betula fontinalis) and box elder (Negundo nuttallii). The number of cases within this group are comparatively few. The second or grass season, commences during April and extends into July. During this season about a third of the patients commence their symptoms. However, there are a large num-

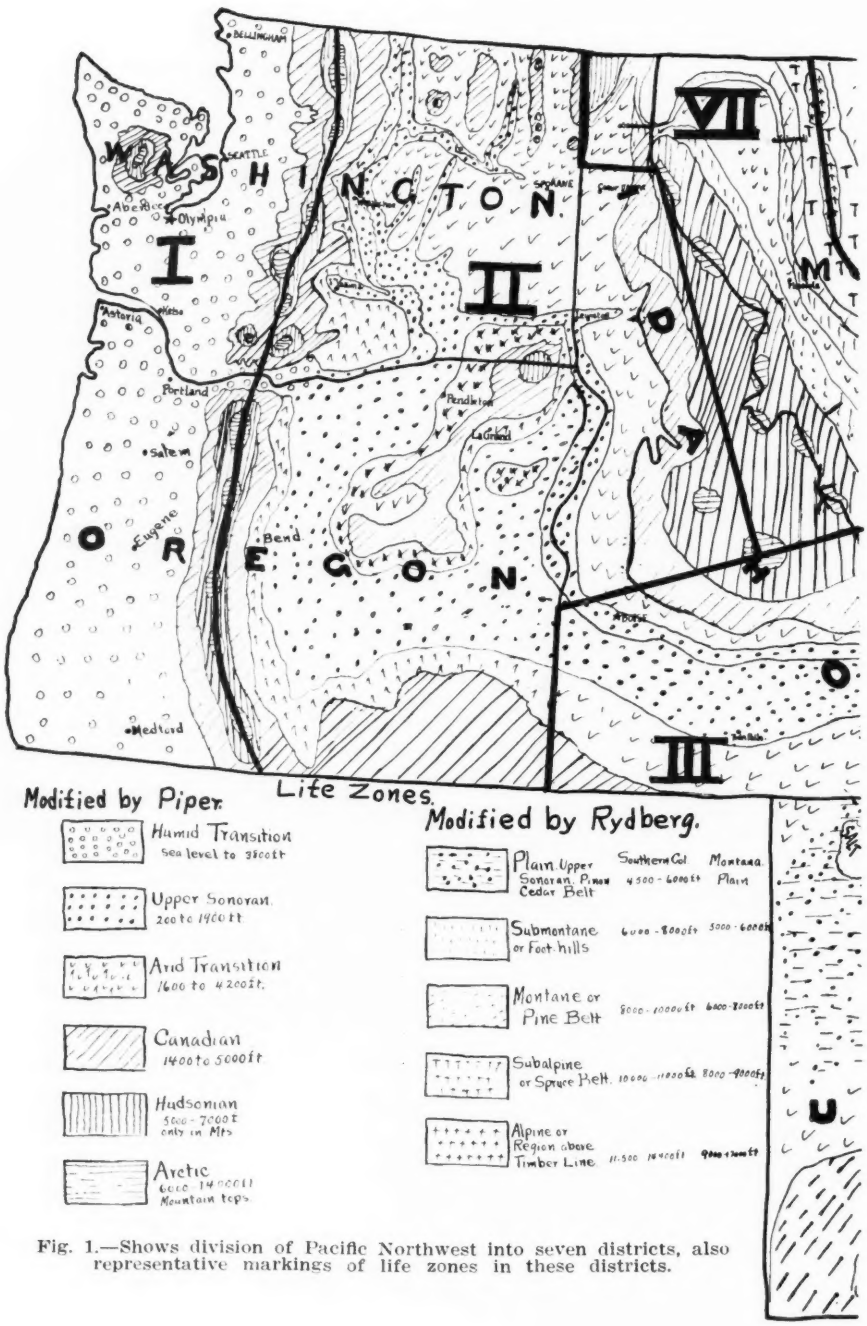

Fig. 1.—Shows division of Pacific Northwest into seven districts, also representative markings of life zones in these districts.

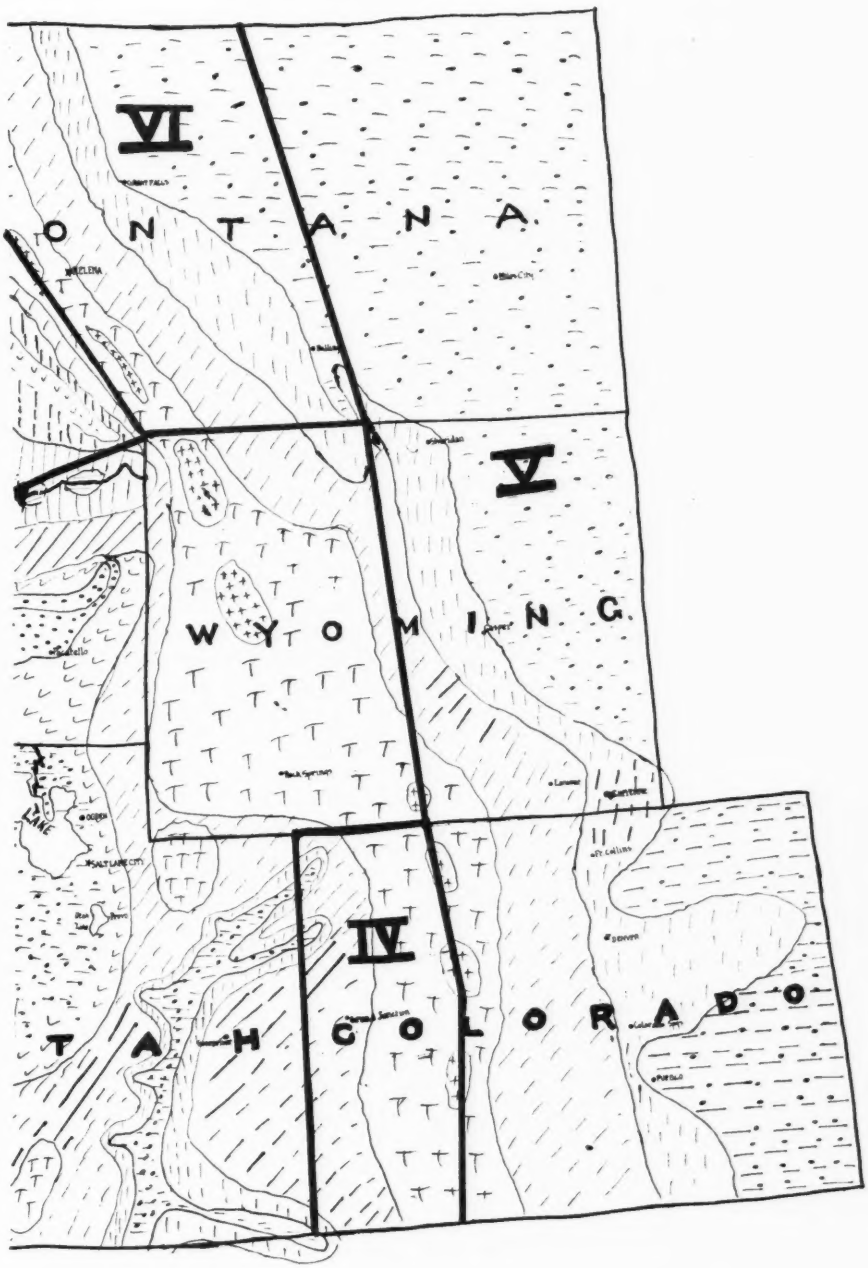
VI
O N T A N A
HELENA
BILLINGS
V
W Y O M I N G
Cheyenne
Laramie
SALT LAKE CITY
IV
C O L O R A D O
DENVER
Colorado Springs
PUEBLO

TABLE I

	COMMON NAME	SCIENTIFIC NAME	DATE OF POLLINATION	WESTERN WASHINGTON AND OREGON	EASTERN WASHINGTON AND OREGON	SOUTHERN IDAHO, WESTERN WYOMING, UTAH	WESTERN COLORADO	EASTERN COLORADO, WYOMING, MONTANA	CENTRAL MONTANA	WESTERN MONTANA AND NORTHERN IDAHO	LIFE ZONE
	TREES										
1	Western Yellow Pine	Pinus ponderosa	June	+	++	+++			++	+++	Arid Transition
2	Lodgepole or Tamarack Pine	Pinus contorta	May and June	+	+				+		Canadian
3	Utah Juniper	Sabina utahensis	April			+++	++				Upper Sonoran
4	California Black Oak	Quercus kellogii	May	+							Arid Transition
5	Garry's or Oregon Oak	Quercus garryanna	May	++							Humid Transition, Sonoran
6	California Hazelnut	Corylus californica	March-April	++							Transition Humid, Arid
7	Spring Birch	Betula fontinalis	March-May	+	++	++	+	+		++	Canadian
8	Thin-leaved Alder	Alnus tenuifolia	March-April	++	++	++	+	+	+	++	Transition, Canadian
9	American Aspen	Populus tremuloides	April-May	++	++	+	+	+	+	++	Canadian
10	Black Cottonwood	Populus trichocarpa	April-May	++	++	+				+	Transition, Canadian
11	Willow	Salix species	March-April	++	+					+	All Zones
12	Box Elder	Negundo nuttallii	April	++	++	++	++	++	++	++	All Zones

TABLE I—CONT'D

	POACEAE	*GRASS FAMILY*								
13	Barnyard Grass	Echinochloa crus-galli	June-October	+	+	+		+		+	Cultivated Soil
14	Green Foxtail	Cheatochloa-viridis	July-September	++	+	+		+		+	Cultivated Soil
15	Needle and Thread Grass	Stipa comata	June-August		+	++	+				Upper Sonoran
16	Indian Mountain Rice	Oryzopsis hymenoides	June-July		+	+	+				Upper Sonoran
17	Timothy	Phleum pratense	June-July	++++	+++	++	++	++	++	+++	Waste Places, Cultivated Soil
18	Little Meadow Foxtail	Alopecurus aequalis	June-July	++	+	++	++	+	+	++	Transition
19	Sand Dropseed	Sprobolus cryptandrus	June-September		++	+++	++	+			Upper Sonoran
20	Red Top	Agrostis palustris	June-August	+++	++	++	+	++	+	+++	Waste Places, Cultivated Soil
21	Velvet Grass	Notholcus lanatus	June-July	+++++							Waste Places, Cultivated Soil
22	Koeler's Grass	Koelaria cristata	June-July		+++	++			+	++	Transition
23	Tall Oat Grass	Arrhenatherum elatius	June-July	++	+						Transition
24	Salt Grass	Distichlis spicata	April-July		+	++	+			+	Plain, Submontane
25	Orchard Grass	Dactylis glomerata	June-July	++++	++	++	++	++	++	++	Waste Places, Cultivated Soil
26	Annual Blue Grass	Poa annua	March-September	++	+	+					Plain, Montane
27	Kentucky Blue Grass	Poa pratensis	May-September	+++++	+++++	+++++	++++	++++	+++	++++	Plain, Submontane
28	Canada Blue Grass	Poa compressa	June-August	+++	++	++	++	+	++	+++	Plain, Montane
29	Sandberg's Blue Grass	Poa sandbergii	May-June		+++	++				+	Arid Transition Canadian

TABLE I—CONT'D

	COMMON NAME	SCIENTIFIC NAME	DATE OF POLLINATION	WESTERN WASHINGTON AND OREGON	EASTERN WASHINGTON AND OREGON	SOUTHERN IDAHO, WESTERN WYOMING, UTAH	WESTERN COLORADO	EASTERN COLORADO, WYOMING, MONTANA	CENTRAL MONTANA	WESTERN MONTANA AND NORTHERN IDAHO	LIFE ZONE
30	Meadow Fescue	Festuca elatior	June-July	+++	++	+++	++	++	+	++	Waste Places, Cultivated Soil
31	Smooth Brome	Bromus inermis	June-July	++	+++	++	+		++	++	Waste Places, Cultivated Soil
32	Soft Cheat	Bromus hordeaceous	June-July	+++	+++	++	++	++	++	++	Waste Places
33	Cheat or Chess	Bromus secalinus	June-July	++	++	+	+	+	+	+	Waste Places, Cultivated Soil
34	Italian Rye Grass	Lolium multiflorum	June-August	++							Naturalized from Europe
35	Perennial Rye Grass	Lolium perenne	June-August	+++	+	+		+		+	Naturalized from Europe
36	Quack Grass	Agropyron repens	June-August	+++	+++	++		+		++	Naturalized from Europe
37	Western Wheat Grass	Agropyron smithii	June-August		+	+++	+++	+++			Upper Sonoran, Transition
38	Giant Basin Wheat Grass	Agropyron inerme	June-July		++++	++++	++	+++			Arid Transition
39	Squirrel Tail	Hordeum jubatum	June-July		+++	+++	++	+++	++	++	Upper Sonoran, Arid Transition
40	Giant Rye Grass	Elymus condensatus	June-August		+++	++		+	+	++	Upper Sonoran, Arid Transition
41	Western Rye Grass	Elymus glaucus	June-August		++	+	+		+	++	Transition
42	Blue Bunch Wheat Grass	Agropyron spieatum	May-June		++++	++++	++				Plain, Submontane
	URTICACEAE	*NETTLE FAMILY*									
43	Lyall's Nettle	Urtica lyallii	June-August	++	+						Canadian, Transition

TABLE I—CONT'D

POLYGONACEAE	*BUCKWHEAT FAMILY*									
44	Sheep Sorrel	Rumex acetocella	May-September	+++	+++	++	++	++	+	++	Plain, Submontane
45	Yellow or Curled Dock	Rumex crispus	June-July	++	++	+	++	++	+	++	Plain
CHENOPODIACEAE	*GOOSEFOOT FAMILY*									
46	Lamb's Quarters	Chenopodium album	June-August	++++	++++	++++	++++	+++	++	+++	Plain, Submontane
47	Mexican Fireweed	Kochia scoparia	August-October				++	+			Plain
48	Australian Salt Brush	Atriplex spatiosa	August-October			+++	+	++			Plain, Sonoran
49	Hastate Atriplex	Atriplex hastata	August-October		+++	+++	++	+		+	Plain, Sonoran
50	Silvery Atriplex	Atriplex argente	August-October		+++	++	+	+			Plain, Sonoran
51	Winter Fat	Eurotia lanata	April-May		+	+++	++	++			Sonoran, Plain, Montane
52	Greasewood	Sarcobatus vermiculatus	May-September		+	++		+	+	+	Sonoran, Plain, Montane
53	Russian Thistle or Salt-wort	Salsola Pestifer	July-September		+++++	+++++	+++	++++	+++	+++	Plain, Submontane
AMARANTHACEAE	*AMARANTH FAMILY*									
54	Redroot Pigweed	Amaranthus retroflexus	June-September	+++	++++	++++	++++	++++	++++	+++	Plain, Submontane
55	Prostrate Pigweed	Amaranthus blitoides	June-September	+++	+++	++	++	++	++	+	Sonoran, Plain, Montane
56	Tumbleweed Pigweed	Amaranthus graecizans	July-September	+++	+++	+++	++	++	+++	++	Plain, Submontane
PLANTAGINACEAE	*PLANTAIN FAMILY*									
57	Broad-leaved Plantain	Plantago major	May-September	++	++	+	+	+	+	++	Plain, Montane
58	English or Narrow-leaved Plantain	Plantago lanceolata	May-October	++++	+	++	++	++	++	++	Plain

TABLE I—CONT'D

	COMMON NAME	SCIENTIFIC NAME	DATE OF POLLINATION	WESTERN WASHINGTON AND OREGON	EASTERN WASHINGTON AND OREGON	SOUTHERN IDAHO, WESTERN WYOMING, UTAH	WESTERN COLORADO	EASTERN COLORADO, WYOMING, MONTANA	CENTRAL MONTANA	WESTERN MONTANA AND NORTHERN IDAHO	LIFE ZONE
	COMPOSITAE	*SUNFLOWER FAMILY*									
59	Poverty Weed	Iva axillaris	May-September		+	++	+	++	+		Plain, Submontane
60	Marsh-elder, Careless Weed	Cyclachaena xanthifolia	July-September		+++	+++	++	++	++	++	Plain, Submontane
61	Giant Ragweed	Ambrosia trifida	August-October					++			Plain
62	Short Ragweed or Bitterweed	Ambrosia elatior	August-October			++		++			Plain, Submontane
63	Western Ragweed	Ambrosia psilostachya	August-September		+	++		++			Plain, Submontane
64	False Western Ragweed	Franseria acenthocarpa	July-September		+	++					Sonoran Submontane
65	Cocklebur	Xanthium canadense	July-September		+	++		+		+	Plain
66	Green Sagebrush	Artemisia dracunculoides	August-October		++			+		+	Plain, Submontane
67	Common Sagebrush	Artemisia tridentata	August-October		+++++	+++++	+++	+++			Plain, Montane
68	White Sagebrush	Artemisia ludoviciana	August-September		+++	+++	++	++		++	Plain, Submontane
69	Pasture Sagebrush	Artemisia frigida	July-October		+	++		++	++	++	Sonoran
70	Mugwort	Artemisia vulgaris	July-September		++	+					Waste Places
71	Dandelion	Taraxacum taraxacum	April-September	+++	+++	+++	+++	+++	+++	++++	Waste Places, Cultivated Soil

ber of this group whose symptoms extend into the late fall and these we find sensitive to some of the weeds that continue pollinating until October. The third season commences about July first and the pollination of this group of plants continues until frost. The weed that is responsible for the largest group of hay fever subjects in this district is Russian thistle (Salsola pestifer). At least 75 per cent of the pollen sensitive individuals react to this pollen. In this group we find many examples of multiple sensitizations, for in this district is an unusual abundance of weeds of all descriptions. Perhaps second in importance as a producer of symptoms are the sages (Artemisia tridentata, dracunculoides, ludoviciana, frigida, vulgaris) and pigweeds (Amaranthus retroflexus, blitoides, graecizans). The lesser factors are marsh elder (Cyclach-aena xanthifolia) and false western ragweed (Franseria acanthocarpa). Where sensitiveness to these weeds exists in any degree, it is necessary to protect that individual for each weed, since the composite group apparently is of such a heterogeneous nature that one of this group will not protect another.

It is a striking fact that the botanical make-up of Eastern Oregon and Washington and Western Oregon and Washington are so entirely different that patients suffering from hay fever can usually find relief in the opposite district. This is strikingly true of the Russian thistle and sagebrush sensitive individuals who as soon as they reach the summit of the Cascades find relief from symptoms west of that range of mountains.

The botanical make-up of District No. 3 compares in a general way with District No. 2, except that in the extreme southeastern portion of Idaho one begins to find evidence of the short ragweed (Ambrosia elatior). It apparently is gaining a foothold and although no factor at this time, later may prove to be of importance. This weed, however, increases in abundance as one goes eastward in the plain and submountain life zones.

Western Colorado, or District No. 4, resembles Districts 2 and 3 in its distribution of the Gramineae, the Chenopodiaceae and the Amaranths. However, probably due to the altitude there is an absence of the Ambrosia in this district and many new species of the Artemisia are encountered.

Eastern Colorado, Eastern Wyoming, and Eastern Montana, or District No. 5, is quite similar to Western Colorado, but as the altitude is generally much lower, we again find both the short and giant ragweed (Ambrosia elatior and trifida) that increase in abundance as the extreme eastern portion of the states is reached and gradually blend with the liberal distribution as found in the eastern states.

Central Montana, or District No. 6 resembles District No. 2 in the occurrence of important hay fever producers. As the altitude is somewhat higher here, the grasses occurring at that altitude are perhaps

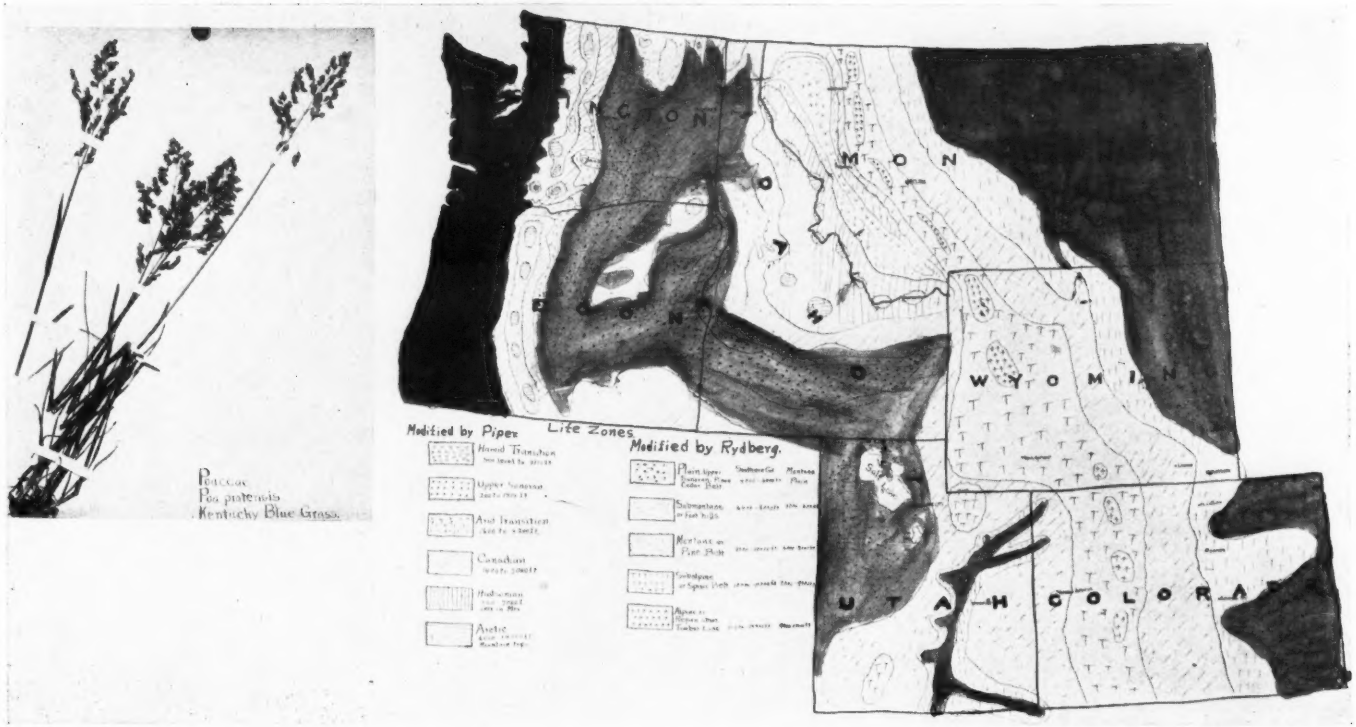

Fig. 2.—Showing specimen and distribution of Kentucky blue grass (Poa pratensis). Distribution is general. Most common in populated districts.

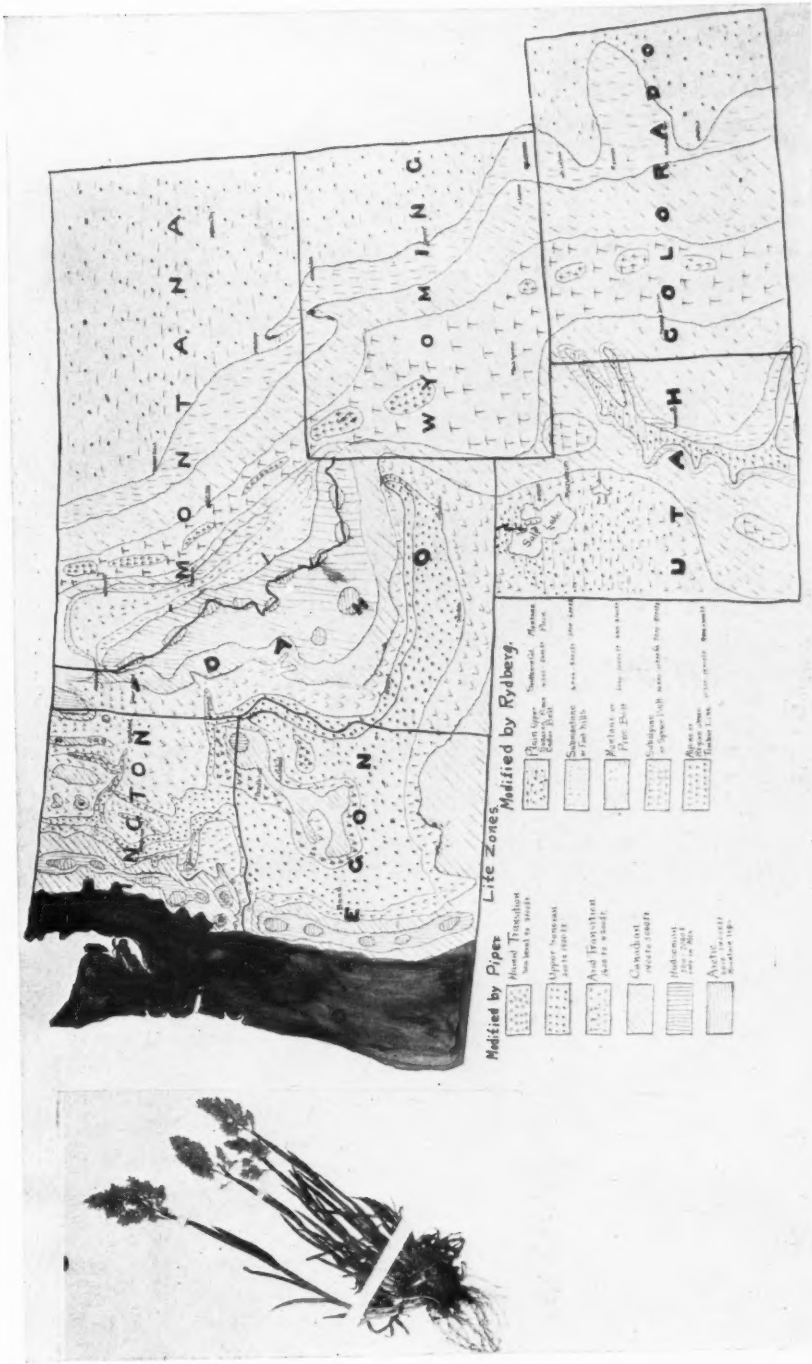

Fig. 3.—Showing specimen and distribution of velvet grass (Notholcus lanatus). Distribution is abundant in District 1.

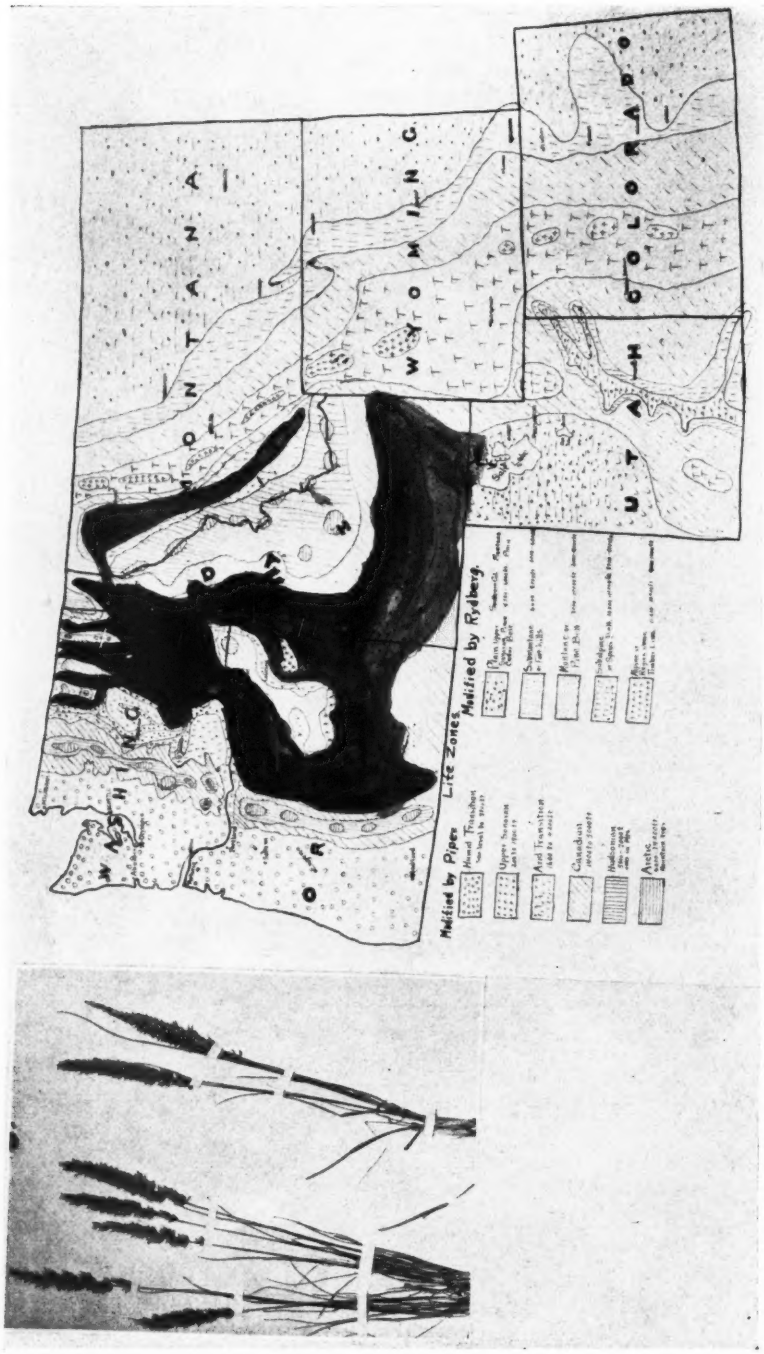

Fig. 4.—Showing specimen and distribution of Koeler's grass (Koeleria cristata). Distribution is confined to Districts 2 and 7 and northern portion of District 3.

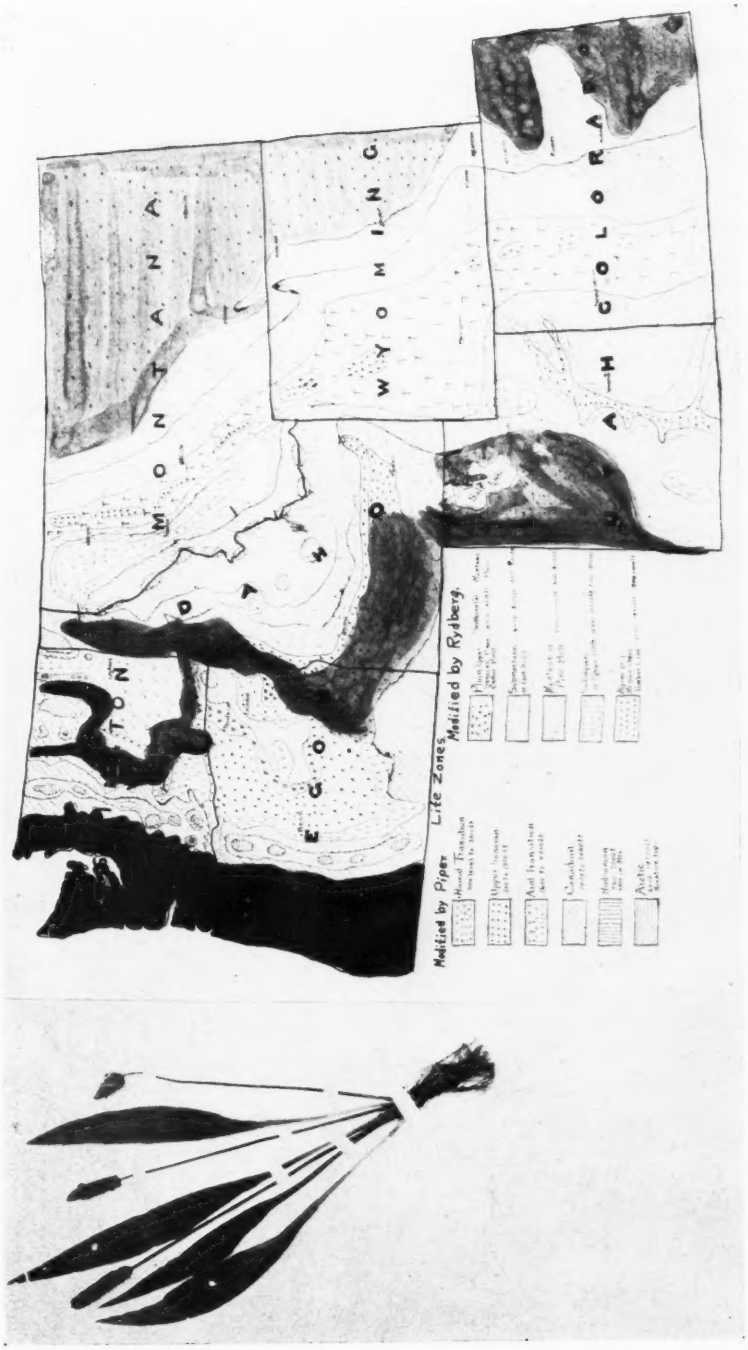

Fig. 5.—Showing specimen and distribution of English plantain (Plantago lanceolata) Distribution is quite general. It occurs on the lawns of populated districts, but grows in abundance in District 1.

Fig. 6.—Showing specimen and distribution of Russian thistle (Salsola pestifer). Very abundant in all districts except District 1 where it is not evident. This weed is responsible for at least 75 per cent of hay fever in the districts where it occurs.

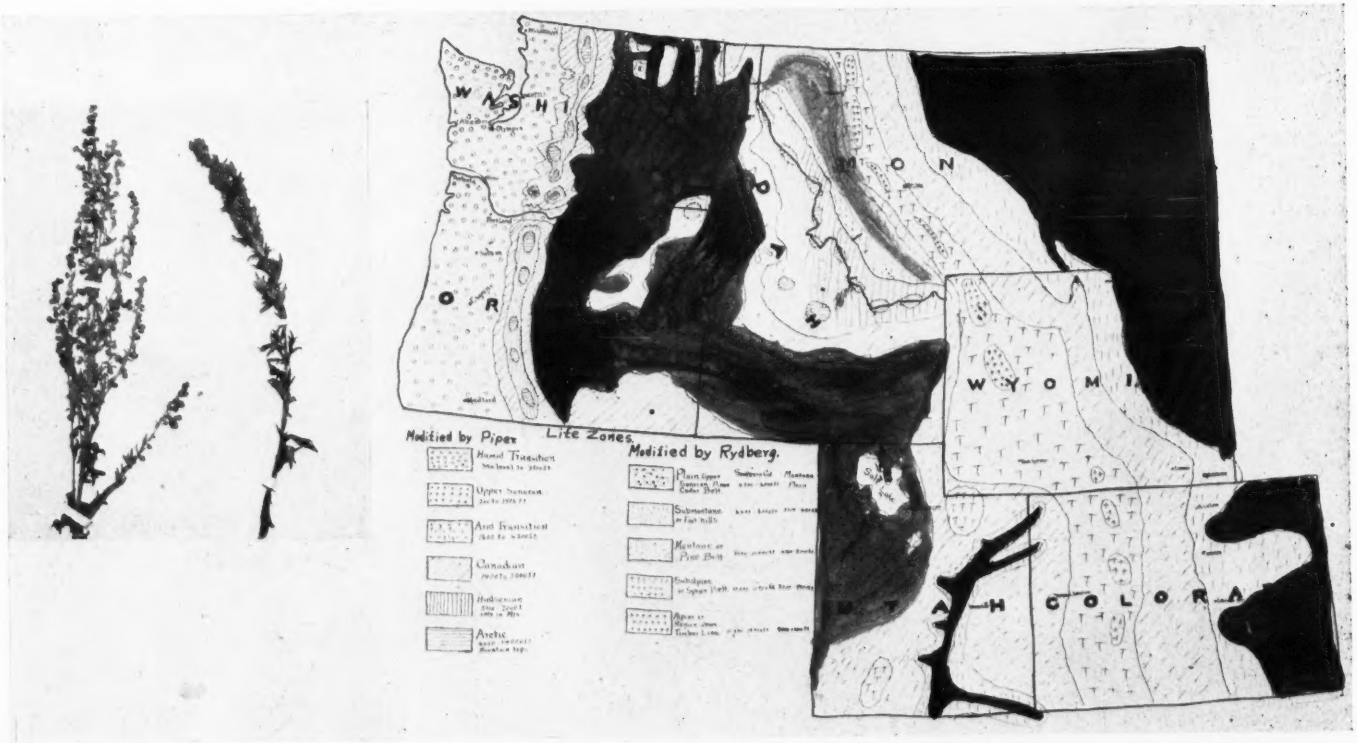

Fig. 7.—Showing specimen and distribution of the sages. Common sagebrush (Artemisia tridentata), white sagebrush (Artemisia ludoviciana). Distribution in the prairie districts of those above shown. District 1 is entirely free of this shrub and patients with this sensitization can live here without symptoms.

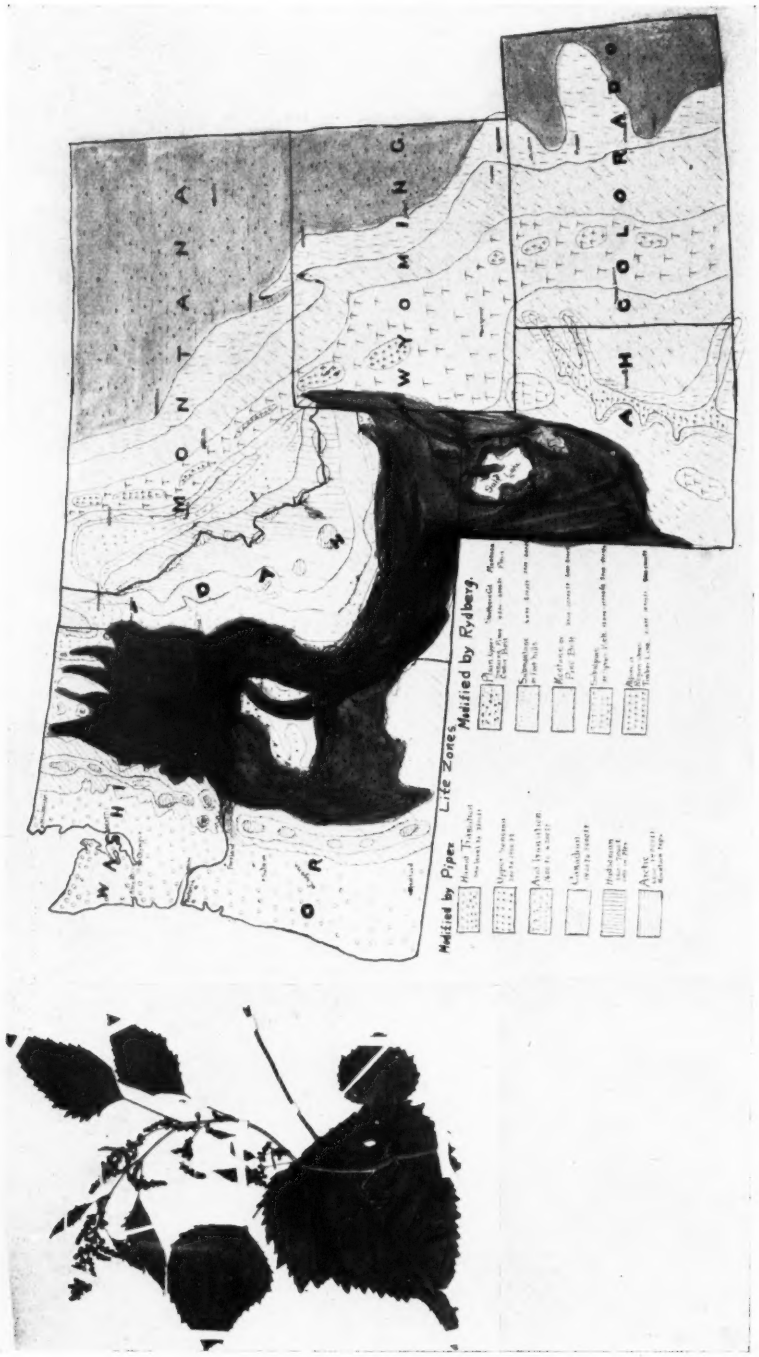

Fig. 8.—Showing specimen and distribution of marsh elder (Iva xanthifolia). Important distribution confined to Districts 2 and 3.

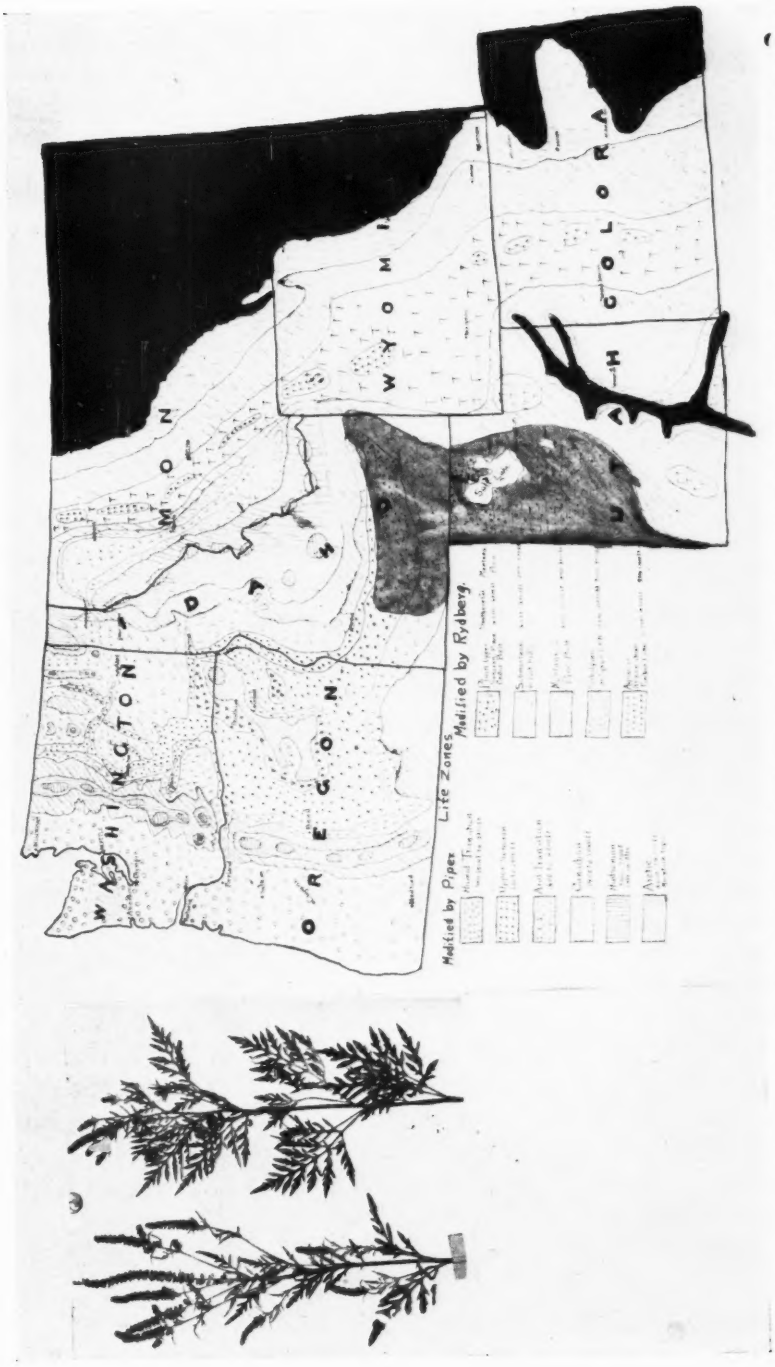

Fig. 9.—Showing specimen and distribution of short ragweed (Ambrosia elatior). Very abundant in District 5, less abundant in Districts 3 and 1. This weed is gaining a foothold in southern Idaho but as yet is not considered a factor. Occasional specimens are reported near Spokane, Washington, and Lewiston, Idaho, but not abundant enough in these localities to produce symptoms.

more plentiful and we find Kentucky blue grass (Poa pratensis), timothy (Phleum pratense) and the brome grasses (Bromus inermis, hordeaceous, secalinus) growing profusely. Russian thistle (Salsola pestifer), pigweeds (Amaranthus retroflexus, blitoides, graecizans) and sages (Artemisia tridentata, dracunculoides, ludoviciana, frigida, vulgaris) are relatively abundant, but in general do not infest as densely as in Central Washington.

Northern Idaho and Western Montana, or District No. 7, is a mountainous country with many broad fertile valleys, making each district an almost individual problem. In a general way, among the trees that occur most commonly are the alders (Alnus tenuifolia), birches (Betula fontinalis). The grasses include timothy (Phleum pratense), red top (Agrostis palustris), Kentucky blue grass (Poa pratensis), Canada blue grass (Poa compressa), and the brome grasses (Bromus inermis, hordeaceous, secalinus), velvet grass (Notholcus lanatus) and the rye grasses (Elymus glaucus, condensatus).

In the higher valleys one does not encounter any of the later pollinating weeds, but in many of the lower valleys, Russian thistle (Salsola pestifer), pigweeds (Amaranthus retroflexus, blitoides, graecizans) and the sages (Artemisia tridentata, dracunculoides, ludoviciana, frigida, vulgaris) occur and are decided factors.

Insect-pollinated flowers as a rule are of importance only in isolated instances and as a rule produce symptoms only by reason of their ability to hold wind-borne pollens. Yet we are forced to the conclusion that one of this vast group is of decided significance in many of these districts and must be considered as a hay fever-producing weed. This flower is dandelion (Taraxacum taraxacum), which is included in the large group of Compositae. It not only grows, or better, replaces our lawns, but is found plentifully along the rocky slopes of Northern Idaho and Western Montana, as well as along the west coast of Oregon. Growing wild the stems are considerably longer, the leaves elongated, and the flower is smaller than those growing in cultivated soil. It is quite difficult to remove the pollen from the flower, but undoubtedly as the seeds fly from the flower a considerable amount of pollen escapes and is carried by the wind. Our records contain many dandelion-sensitive individuals, some of whom react only to the extracts of dandelion and are entirely relieved of their symptoms by desensitization with an extract of dandelion pollen.

SUMMARY

In summarizing, I wish to emphasize the following points:

1. A survey of the principal hay fever-producing plants within the Pacific Northwest subdivides this territory arbitrarily into seven districts.

2. A comparative and detailed chart is presented to show the relative abundance of the various wind-pollinated plants that are found in each district.

3. It is a significant fact that in each district certain plants can be anticipated because of the life zones that are contained in that district.

4. A wide variation of plant life exists in each district and it is therefore necessary to know the existing plant life in order intelligently to test the individual whose hay fever develops in that district.

5. Dandelion, although an insect-pollinated plant, must be considered a factor in the production of hay fever symptoms.

(The authors wish to thank Mrs. F. J. Bahrenberg for her help in preparing the illustrative charts of this paper.)

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CINCHOPHEN POISONING IN ALLERGIC INDIVIDUALS*

Report of Two Cases

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ATTENTION has been directed recently to the frequent occurrence and the seriousness of cinchophen poisoning.[1] In some patients, symptoms follow the exhibition of as little as one gram of the drug, while others tolerate huge doses over long periods of time. A patient now under observation has been taking cinchophen in doses as large as 9 grams a day periodically for three years with no untoward effects. Since this drug is so generally used, and the cases of poisoning are so relatively few, it seems possible that the susceptibility to its toxic action may be an allergic phenomenon.

Coca[2] differentiates between toxic symptoms following an overdose of a drug, and those symptoms produced by an allergic reaction to it as follows: when the symptoms are merely exaggerations of the physiologic action, the reaction is purely toxic; when the symptoms differ sharply from the usual action, or bear little or no relation to the normal action, the reaction is allergic.

Two cases of cinchophen poisoning which we observed recently, have occurred in patients with active allergy to other substances, and the symptoms when analyzed in accordance with Coca's dictum have semed to be allergic in nature. Since a search of the literature discloses no mention of the allergic history in the reported cases, these cases are reported to direct attention to this factor in the etiology.

Case 1.—A white male, aged forty-seven, a salesman, was admitted to the service of Dr. Milton Cohen, November 4, 1928, complaining of jaundice and itching. He had been fairly healthy up to five years previous to admission, with the exception of typhoid fever when six years old. He has had asthma for the past five years and was found sensitive to feathers; horse, dog, and cat hair; wool, rice, banana, and celery.

About six weeks before admission, he began having dull pain in his right knee and a few days later, a similar pain was noticed in the right shoulder and hand. A physician prescribed cinchophen, 0.5 gram, four times daily for this pain. About three weeks later, after a total of 12 grams were taken sporadically during this time, he developed hives, and one week thereafter, a painless jaundice appeared togther with marked itching and some purpuric spots on the extremities. At this time cinchophen was discontinued.

Physical examination revealed a well-developed, moderately undernourished white man, restless because of intense, intractable itching. The temperature was 97.5° F.; the pulse 84; respiration 25; the blood pressure 118/80. There was a marked

*From the Medical Service of the Mt. Sinai Hospital, Cleveland, O.

icteric tint to the skin and the sclerae. Many scratch marks were on the skin of the trunk and a few purpuric lesions were scattered on the arms and legs. The chest was moderately emphysematous in type; breath sounds were clear. The liver edge was just palpable below the costal margin and was slightly tender. The spleen was not palpable.

Laboratory Findings.—R.B.C., 4.5 million; Hg., 80 per cent; W.B.C., 8000; P.M.N., 66 per cent; S.M., 26 per cent; L.M., 7 per cent; Bas., 1 per cent.

Blood chemistry: Glucose 87 mg. per 100 c.c.; nonprotein nitrogen, 27 mg. per 100 c.c.

Van den Bergh test gave a delayed direct and indirect positive; quantitative test, 7.5 units bilirubin. The Wassermann and Kline slide tests were negative.

Urine: Bile pigments, ++; urobilinogen, +; urobilin, +; bile salts, ++. The liver Widal test gave a normal response.

Subsequent Course.—The patient slowly improved, jaundice and itching disappearing in about ten days. On May 22, 1929, a skin test with a 1:1000 solution of cinchophen was strongly positive.

CASE 2.—A white male, aged fifty-four, was admitted to the service of Dr. Milton Cohen, March 9, 1929, complaining of hives. This patient had enjoyed good health in general, but had noticed that he was subject to attacks of hives following the ingestion of strawberries. There was no history of hay fever or asthma. The patient's father was asthmatic.

The patient ate strawberries for lunch on two successive days. On the third day he developed a pain in the right shoulder and elbow which he called rheumatism, and on the advice of a friend he took 1 gram of cinchophen three times a day for nine days. On the day before admission he noticed the sudden appearance of a profuse crop of hives with intense itching over his body. No strawberries had been eaten for eight days.

Physical examination showed a well-developed, slightly obese male, extremely uncomfortable because of itching. There were many large urticarial wheals on the extremities and abdomen. A slight photophobia was present but no evident icterus. The glands were not enlarged. The chest was barrel-shaped with very little expansion on inspiration. No abdominal tenderness or masses were detected and the liver edge was not palpable.

Laboratory Tests.—R.B.C., 4.1 million; Hg., 70 per cent; W.B.C., 6,900; P.M.N., 80 per cent; S.M., 10 per cent; L.M., 8 per cent; Eos., 2 per cent.

Blood chemistry: Glucose, 172 mg. per 100 c.c.; nonprotein nitrogen, 21 mg. per 100 c.c. Van den Bergh test gave a delayed direct and a positive indirect action. The quantitative test gave 0.85 units bilirubin. Urine: Urobilinogen, +; bile pigments, ±; bile salts, 0. Microscopically, an occasional erythrocyte and leucocyte were found.

Subsequent Course.—The patient was treated with frequent small injections of epinephrin and gradually improved. On June 2, 1929, a skin test with a 1:1000 solution of cinchophen was strongly positive.

DISCUSSION

The asthmatic history in Case 1, together with the positive skin tests and the control of the symptoms by avoidance of the offending allergens leaves no doubt as to the diagnosis of allergy. The cinchophen poisoning is considered merely another allergic manifestation in this individual.

Case 2 does not give a clear-cut history. However, he is known to be allergic to strawberries and has a family history of allergy. Whether the joint symptoms represented a manifestation of allergy to strawberries or not cannot be determined, but every allergist of experience has seen joint symptoms of allergic origin either alone or combined with other allergic manifestations. The urticarial symptoms and the latent jaundice followed the taking of cinchophen, and after recovery the patient was shown to be allergic to cinchophen.

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THE VALUE OF CALCIUM IN ASTHMA, HAY FEVER AND URTICARIA*

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BECAUSE of the traditional idea that a deficiency of blood calcium exists in so-called allergic diseases, and that calcium therapy is indicated in the treatment of these conditions, a series of observations was started in 1920, in order to determine the true value of calcium in asthma, hay fever, and urticaria. The statistics and opinions expressed in this report are based on a study of 150 cases: 50 cases of asthma, 50 of hay fever, and 50 of urticaria. A great many more cases have been studied from this angle, but for purposes of simplicity in drawing up statistics, 150 cases were picked at random from the several hundred completed records. Only those cases showing at the initial examination a blood calcium of less than 10 milligrams per 100 c.c. of blood were selected for this report. At this time it may be well to state, without going into lengthy detail, that a review of a very large number of determinations of blood calcium in asthma, etc., has failed to show a consistently marked deficiency. The vast majority had a blood calcium above 10 milligrams and quite a few above 10.5 milligrams; and furthermore, as will be shown by the charts herein published, the administration of calcium, or calcium and phosphorous, did not influence the symptoms or course of the disease in a single case, even though the blood calcium was actually increased.

It is quite apparent from a study of Table I that in most cases there was a definite influence on the amount of blood calcium. However, in not a single case was there any demonstrable clinical beneficial effect. This is also true of cases having a high calcium (above eleven) at the initial examination, and whose calcium was raised even higher. The accompanying figures show that there seems to be no definite reaction trend; some were higher on the second determination, others were lower. Some continued increasing for eight weeks, others returned to their original level, etc. Any number of cross statistical tables have been drawn from the accompanying list, but were omitted because they would serve only to confuse the reader. For the same reason and for the sake of eliminating tables of useless figures, I am omitting a detailed report of the calcium figures in the 50 cases of hay fever and the 50 cases of urticaria. I shall give only the conclusions and impres-

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sions of a review of these figures which parallel very closely those printed in Table I for asthma.

A great many cases of hay fever and urticaria showed normal or higher than normal calcium values, but only 50 of those having cal-

TABLE I

DETERMINATIONS IN ASTHMA. EVERY CASE WAS OF THE SPECIFICALLY HYPERSENSITIVE TYPE

CASE	FIRST DETERMINATION*	SECOND DETERMINATION	THIRD DETERMINATION
1.	8.2	8.0	8.4
2.	8.0	8.0	7.8
3.	7.2	8.5	8.0
4.	7.2	8.5	9.8
5.	7.6	9.5	9.5
6.	8.5	8.0	9.2
7.	9.0	9.2	9.2
8.	9.2	8.8	9.2
9.	9.5	10.0	10.4
10.	9.4	10.2	11.0
11.	9.0	8.8	9.8
12.	8.2	9.0	10.5
13.	8.2	8.0	8.0
14.	9.8	9.8	9.8
15.	9.0	8.2	9.5
16.	9.0	9.8	10.4
17.	8.0	10.6	11.8
18.	8.2	11.2	11.0
19.	8.8	9.6	9.8
20.	9.0	9.0	9.4
21.	7.6	9.8	9.0
22.	8.6	9.0	9.2
23.	7.7	7.7	8.4
24.	7.8	7.4	7.9
25.	9.2	9.0	9.8
26.	9.2	9.4	11.2
27.	8.3	8.5	8.6
28.	8.2	8.0	8.4
29.	8.0	8.0	8.2
30.	8.0	8.2	8.0
31.	7.2	7.8	7.7
32.	7.2	7.4	7.4
33.	6.5	7.0	7.4
34.	6.5	6.8	8.0
35.	9.1	8.4	9.0
36.	7.0	7.4	8.8
37.	6.8	8.0	8.0
38.	6.2	8.0	8.2
39.	7.0	7.4	9.0
40.	7.2	10.0	10.5
41.	8.0	8.5	9.3
42.	8.2	11.0	11.5
43.	9.0	8.8	9.4
44.	9.8	9.0	9.5
45.	9.4	9.8	9.8
46.	7.4	8.0	8.6
47.	7.0	8.5	11.2
48.	6.4	10.0	10.4
49.	7.5	9.0	9.8
50.	7.0	8.2	8.2

*First determination was at the initial visit before treatment.
Second determination was four weeks after starting administration of calcium.
Third determination was eight weeks after starting administration of calcium.

cium values below 10 milligrams were chosen for this report. As a whole, the hay fever cases showed a higher initial calcium figure than the asthma and urticaria cases, and the urticaria cases lower on an average than the asthma cases. The general response to calcium preparations was similar to that shown in the asthma series, and the clinical result was the same.

It is my conviction that calcium is of very little clinical value in the treatment of asthma, hay fever, and urticaria. These conclusions agree with those of Criep and McElroy,[1] but are at variance with the opinion of many others, notably Sterling,[2] Brown and Hunter,[3] Pottenger,[4] Novak and Hollender,[5, 6] Patterson.[7]

The work recently published by Myers[8] regarding so-called vagotonia and sympatheticotonia is well worth careful consideration by those interested in this phase of the asthma problem.

In stating that I have not seen clinical improvement following the raising of blood calcium in allergic conditions, I do not mean to imply that some cases have not shown temporary improvement. This is particularly true in urticaria, but the improvement does not last long and may have been occasioned by many other factors unrelated to calcium administration. Calcium has been used in this series in the form of vigantol, calcium lactate, and afenil. We have also observed the effect on the blood calcium of the quartz lamp and of the combined administration of calcium and phosphorous and also of calcium, phosphorous, and parathyroid and thyroid extract; and, again, not desiring to fill pages with unnecessary lists of figures and graphs, I repeat that there is no change in my stated opinion of the value of these drugs and combinations, in the treatment of allergic conditions.

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POLLENS WHICH CAUSE HAY FEVER IN SOUTH CENTRAL TEXAS*

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THERE are numerous plants growing in south central Texas which are given credit for causing the distressing symptoms of hay fever, asthma, and other allergic conditions. The vegetation in this part of Texas is extremely prolific during nine months of the year and particularly so after the spring and fall rains. The period from the middle of December until the middle of March is the low season for vegetation. During this period frosts and freezing temperatures are frequent.

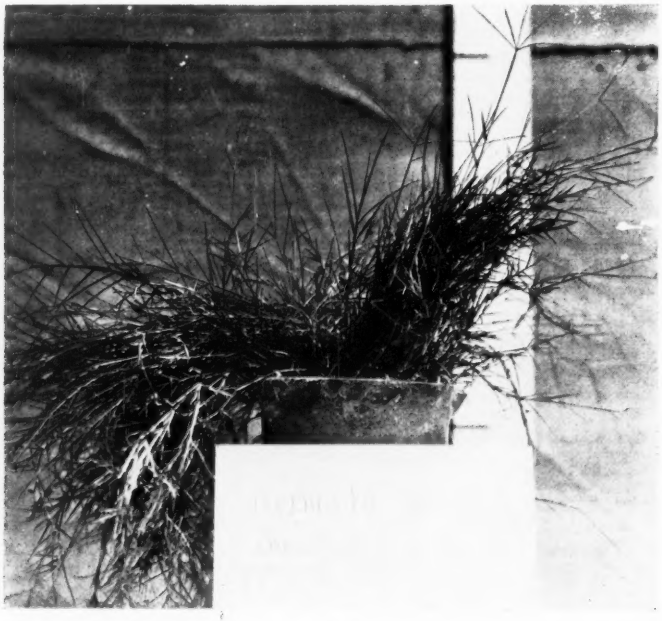

Fig. 1.

During the years 1927, 1928, and 1929 at the Asthma and Hay Fever Clinic, Station Hospital, Fort Sam Houston, we have had the opportunity to test hundreds of hay fever sufferers. We have found that, although there are a great number of pollens which are accused of causing hay fever, in reality there are comparatively few. In fact, our experience shows that by far the greatest amount of suffering is

*From the Asthma and Hay Fever Clinic, Station Hospital, Fort Sam Houston.

caused by pollens from the following plants: viz., the grasses, the ragweeds, the careless weed, plantain, and mountain cedar. We do not contend that some of the minor pollens do not cause hay fever, but we do contend that they are the exception rather than the rule. The following is a list of plants credited with causing hay fever in this part of the state. Those which we have definitely hooked up as offenders are termed major offenders while the others are termed minor offenders.

Fig. 2.

Major Offenders	*Minor Offenders*	
The grasses, principally Bermuda and Johnson.	Cottonwood.	Russian thistle.
The ragweeds, both giant and dwarf.	Shad scale.	Annual saltbush.
The careless weeds, especially *Amaranthus retroflexus, A. palmeri* and *A. blitoides.*	Mesquite (Algaroba).	Western water hemp.
Plantain, of which there are a number of varieties, the *B. occidentalis* being the most common.	Ligustrum.	Marsh elder.
Mountain cedar.	Rabbit bush.	Certain other trees.
	Sheep sorrel.	
	Yellow dock.	
	The sages.	
	Cocklebur.	

The major offenders only will be taken up somewhat in detail.

The Grasses.—Of the grasses, there have been over one hundred species already identified and classified within the city limits of San

Table I

Summary of the Hay Fever Cases for the Seasons 1927, 1928, and 1929, at the Asthma and Hay Fever Clinic, Station Hospital, Fort Sam Houston, Texas

Number of Patients Sensitive to Major Offenders

1 = The Grasses. *2 = The Ragweeds.* *3 = The Careless Weeds.* *4 = The Plantains.* *5 = Mt. Cedar.*

	SINGLE SENSITIVITY					DOUBLE SENSITIVITY						TRIPLE SENSITIVITY				QUADRUPLE SEN.	
	1	2	3	4	5	1-2	1-3	1-4	1-5	2-3	2-5	1-2-3	1-3-4	1-2-4	2-3-4	1-2-3-4	1-2-3-5
1927	13	18	1	0	0	22	4	0	0	5	0	12	0	0	0	0	0
1928	17	12	1	0	0	19	3	0	1	5	0	11	0	0	0	0	0
1929*	14	11	1	0	0	13	2	0	2	7	2	9	1	1	1	2*	1

*To September 1 only.

Table II

Percentage of Patients Sensitive to Major Offenders

	GRASS	RAGWEED	CARELESS WEED	PLANTAIN	MT. CEDAR
1927	40%	44.0%	16.0%	Not used	Not used
1928	40%	36.0%	23.2%	Not used	0.8%
1929*	35%	36.7%	18.7%	3.9%	5.5%

*To September 1 only.

Antonio. And this is probably only a start. The principal grasses from a hay fever standpoint are Bermuda and Johnson.

There are two almost distinct grass seasons. The first starts about the middle of March and continues on into July, depending upon the amount of spring rains. After the first of July and until early fall, rains are the exception. During this dry season the grasses die down and their pollen content in the air drops comparatively low. Usually between the first and fifteenth of September the first fall rains come. This rain brings the grasses to renewed life, and they again pollinate in profusion until frost. This usually occurs about the middle of December. During the dry summer period (July and August) there

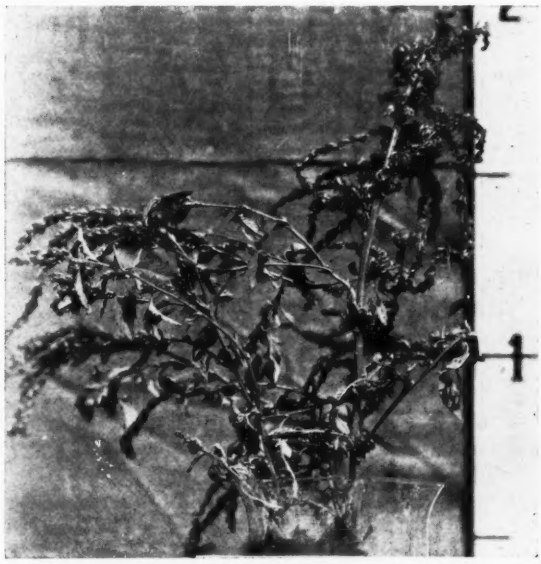

Fig. 3.

is, of course, some grass pollination, particularly in the cities where Bermuda is used almost exclusively for lawn grass and is watered regularly.

The Ragweeds.—Both the giant and dwarf ragweed are present in this vicinity. The giant variety because of its great size is much more conspicuous than the dwarf variety, but I believe that plant for plant, the dwarf will greatly outnumber the giant. The giant variety blossoms much earlier than the dwarf. Usually we do not expect much trouble from ragweed until after the first fall rains. In 1929, however, probably due to the excessive spring rains, the giant ragweed was first seen in blossom on July 29. The dwarf ragweed did not get into full blossom until after the first of October. From the time of the first blossoms of the giant ragweed until after some rain during the

first part of September, it struggled against the drought to keep its head up. Its pollination during this period was extremely limited. Usually there is practically no ragweed pollination until the first part of September. From then on until frost, this plant causes a great deal of suffering.

The Careless Weeds.—A number of varieties of the Amaranthus are present and vary from the A. retroflexus, which grows as high as eight feet to the A. blitoides, which is the small creeping variety. The careless weed begins to pollinate around the first of May and continues

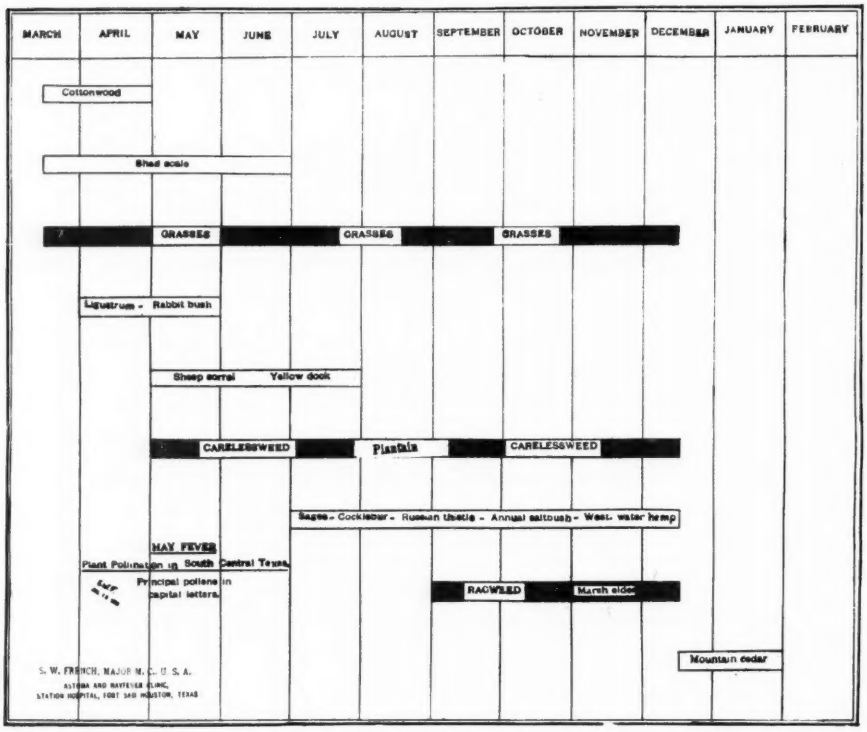

Fig. 4.—Duration of pollination of hay fever-producing plants in south central Texas.

until frost. Like the other offenders it is not so prolific during the dry season but pollinates with renewed vigor after the first fall rains.

The Plantains.—There are a number of plantains in this vicinity. None of them appear to be either the typical English (narrow leaf) or the typical American (broad leaf) variety. The most common variety seems to be a combination of the two. It has more the leaf of the English and the flower of the American plantain. It blossoms at about the same time as the careless weed. In 1929 no plantain was found after the first of July but the previous year (1928) it was found after the fall rains. This plant will have to be observed further before we can classify it as a short or long season offender.

Mountain Cedar.—About the middle of December when the air is almost cleared of the summer pollens, the mountain cedar begins its work. It pollinates from about the middle of December until the first of February. In this vicinity a great deal of use is made of this plant at Christmas time for decorating schools, churches, and homes, both as Christmas trees and as cut branches. Numerous persons date the beginning of their hay fever on Christmas morning.

A tentative pollination chart (Fig. 4) for the vicinity of San Antonio is included with this report, together with photographs of some of the major offenders gathered within the city limits.

Society Proceedings

THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

MIDWINTER MEETING, NEW YORK CITY, DECEMBER 7, 1929

Abstract of Proceedings

The Treatment of Ocular Tuberculosis With Tuberculin.*† LESLIE N. GAY, BALTIMORE, MD.

The successful use of tuberculin in the treatment of ocular tuberculosis has been challenged by a number of internists as well as by ophthalmologists. There is undoubtedly some justification for this scepticism, as it is unanimously agreed that tuberculin, if improperly given, can do far more harm to the eye than good. For a number of years I have been interested in the treatment of this disease, and the results of the treatment of a selected group of patients have been so gratifying that publication of them might be instructive.

The purpose of this paper is to present a clinical report of the methods of diagnosis and treatment used in the Wilmer Clinic of the Johns Hopkins Hospital, and to report the results of such treatment in a selected group of 30 patients. This group of patients is noteworthy because, with two exceptions, each patient had been examined and treated in various other clinics. Complete medical survey had been made before admission to the Wilmer Clinic; all discoverable foci of infection had been eliminated before the patients came under observation; and the majority of these patients had been given the discouraging advice that nothing further could be done. Incidentally both proponents and opponents of tuberculin therapy had treated them, and in several instances tuberculin had been tried in a haphazard way to relieve the condition without results.

In this group of patients, 15 suffered with generalized uveitis, a choroiditis, or a chorioretinitis, 8 with keratitis, 1 with tuberculous nodular scleritis, 1 with iritis, and 5 with recurrent intraocular hemorrhages. The use of tuberculin in any of these types is indicated if sensitiveness to tuberculin is established, and if improved hygiene and removal of foci of infection fail to bring about improvement. The group of patients presented in this report were carefully surveyed before tubercu-

*This paper will be published with the protocols together with a detailed discussion of the theoretical phases of the problem in the Archives of Ophthalmology at some future date.

†From the Wilmer Institute of Johns Hopkins Hospital, Baltimore.

lin therapy was considered. As mentioned above, in all except 2 members of this group, all foci of infection had been eradicated before they came under observation. Survey failed to reveal either fresh foci of infection or any concurrent disease which might explain the ocular condition.

Method of Diagnosis.—The method of diagnosis is by no means new. The patients in this report have been tested by the intradermal technic using the original tuberculin (O. T.) of Koch. This tuberculin has been prepared in the Henry Phipps Tuberculosis Laboratory of the Johns Hopkins Hospital (Willis, H. S., Laboratory Diagnosis and Experimental Methods in Tuberculosis, Springfield, Illinois, Chas. C. Thomas Publishing Company). It is standardized as equivalent to 1000 mg. of tuberculin to 1 c.c.

The sensitivity of the patients is determined by specific dilutions. It is necessary to use a control solution in order to rule out possible reactions to the media. One-tenth c.c. of 1:1000 dilution of the control media is injected intradermally under sterile precautions at a site on the forearm near the wrist. A tuberculin syringe is used. At the same time 0.1 cc.. of 1:100,000 dilution of old tuberculin is injected about three inches from the control on the same arm. The actual amount of tuberculin injected is 0.001 mg. If there is no reaction within forty-eight hours, a second injection is given, consisting of 0.1 c.c. of 1:10,000 dilution (0.01 mg.) of tuberculin. If the patient fails to react to this dilution within forty-eight hours, further injections are given until it is definitely established that the patient will not react to a full milligram of tuberculin. It is important to mention that in my experience it has been unusual to find a skin which reacts to the control solution.

Interpretation of Reactions.—A positive reaction consists of infiltration and hyperemia about the site of injection. It appears in from six to eight hours, reaches its maximum between twenty-four and forty-eight hours, and disappears in from five days to six months. The simplest method of recording the results is to measure the width of the infiltration and the hyperemia after forty-eight hours.

The Method of Treatment.—The method used in the treatment of ocular tuberculosis depends upon the attitude of the physician treating the disease. If a nonspecific form of treatment is desired, the method which I have used is wrong. In nonspecific treatment, a violent constitutional as well as a focal reaction is produced, whether it is in the eye diseased by tuberculosis or in the joints of an individual suffering with arthritis. The result of such a method applied in the treatment of ocular tuberculosis has often been so disastrous that enucleation of the diseased eye has been necessary.

The bouillon filtrate of Denys, a very stable material $\frac{1}{10}$ as strong as the O. T. diagnostic preparation, is used in the treatment. Many

physicians prefer a bacillus emulsion. It is my opinion that the emulsion is responsible for many failures as well as for bad focal reactions. An emulsion of tubercle bacilli contains, for example, a million minute particles in 0.1 c.c., and it is impossible to dilute the material accurately when one deals with a dilution as high as one part in 10,000,000. In other words, one dilution may contain 999 particles when it should contain only 9 particles. This inaccuracy cannot occur when one is diluting a filtrate. The bouillon filtrate has therefore been routinely used in the treatment of these patients.

The initial dose in most instances is 0.000001 mg. of tuberculin injected into the deltoid muscle. The concentration is gradually increased over a period of from six to ten months, depending upon the tolerance of the patient, until a maximum dose of 100 mg. is given.

The treatment is given twice each week until a concentration of 1 mg. per c.c. is reached, at which time it is given once each week. By this method nearly a year is required to complete the treatment. In some instances a longer time is necessary, depending on the behavior of the eye. Careful and frequent observation of the eye by an ophthalmologist is one of the most important features of the method. A focal reaction is a warning that damage is resulting from a too rapidly increased dosage of tuberculin therapy. Under such circumstances the subsequent doses of tuberculin should be reduced to a level of safety. After a dose of 100 mg. has been reached, it is advisable to continue this dose at weekly intervals for a period of months in order that recurrences may be aborted.

SUMMARY

To summarize briefly the salient features of this report, 30 patients suffering with ocular tuberculosis have been treated with the tuberculin of Denys. The use of minute doses of O. T. tuberculin (0.001 mg.) in the diagnosis of the disease is more accurate and safer than is the use of large doses (1 to 5 mg.). The treatment consists of subcutaneous injections of bouillon filtrate, beginning with 0.000001 mg. and gradually over a period of months reaching a maximum dose of 100 mg. The use of bacillus emulsion leads to inaccuracy because of the infinitely small dilutions which are made in this treatment. The constant observation of the eyes is of greatest importance. A focal reaction should be avoided; if it occurs, the subsequent dose should be reduced to a level of safety. The group is considered a selected group because these patients had been treated unsuccessfully by other ophthalmologists before they were admitted to the Wilmer Clinic. In the clinic no abnormality was found, other than tuberculin hypersensitivity, to account for the disease. The use of tuberculin should never be considered in the treatment of the eye unless all foci have been removed. It should be used if after a lapse of from three to six months

the removal of infection fails to bring about improvement. The result of the treatment in these 30 patients has been improvement in vision with the arrest of a disease which ultimately would have blinded the patient.

THE ASSOCIATION FOR THE STUDY OF ALLERGY

SEVENTH ANNUAL MEETING, PORTLAND, OREGON, JULY 8, 1929

A Botanical Survey of Hay Fever-Producing Plants in the Pacific Northwest. ROBERT F. E. STIER, SPOKANE, WASHINGTON. (For original article, see page 260.)

DISCUSSION

DR. GEORGE PINESS, LOS ANGELES.—There are several points that I should like to call to Dr. Stier's attention. I believe that all of us who are doing this work should once and for all make up our minds that we are going to have a standard classification. I think Abrams has a standard classification which has not been carried out here.

Another thing which I want to bring to your attention is that in the publication of such articles, let us use technical terms instead of common names. For instance, you have prairie ragweed (Artemisiaefolia) marked false ragweed. That is not false ragweed in California. I think that if we get together and decide on the nomenclature and use the Abrams classification for a standard, we shall all understand each other, because common names in one vicinity mean nothing in another.

As for distribution of various flora mentioned, it is very interesting to note that the mountainous regions are usually free from most grasses and common offenders. That is true in most parts of the country. I do not believe it is limited to the Northwest. Our people in California and Arizona, when going into the mountains, are usually free. Those things growing in the mountains, such as firs and pines and the various trees, are harmless and there is very little flora that is pollen-bearing.

MR. O. C. DURHAM, INDIANAPOLIS.—I should like to ask Dr. Stier concerning the tumbleweed and pigweed. I have not found that they produce an offending quantity of pollen in the central states. I find that the giant ragweed and the short ragweed do not appear out this way beyond the Rocky Mountains. I did find in Boise some specimens which I took to be Franseria, but they were not in bloom yet, so I could not be positive. In Cheyenne, Franseria is very common.

As to the dandelion, I should like to ask Dr. Stier if he has ever plated to find dandelion pollen. I should like to have that as final proof that dandelion is the real factor.

During the past winter a man who is ragweed sensitive and has taken pollen treatment became excited and wrote to the laboratory, stating that on two occasions he drank some dandelion wine and had perfect reproductions of the symptoms of hay fever. He wanted to know whether it would be necessary for him to be treated with dandelion extract. I told him to put away the dandelion wine, because it was dandelion pollen extract that he was drinking.

DR. GEORGE PINESS.—May I correct Mr. Durham? One can collect barrels of brome pollen. If you would like some, we shall be glad to give it to you.

MR. DURHAM.—We do not have it in the East.

DR. RAY M. BALYEAT, OKLAHOMA CITY.—Clinically, I do not believe that the dandelion will cause hay fever. I quit testing with it a long time ago. I am sure that 80 or 90 per cent of all the people who are sensitive to ragweeds will also be sensitive to dandelion, because it is in the same family. These people who are ragweed sensitive and are also sensitive to dandelion do not have symptoms in the spring of the year when their lawns are covered with dandelions and remain covered for two or three weeks. If they have symptoms from dandelion, they ought to have symptoms then. I do not believe enough pollen gets into the air to produce symptoms clinically.

I was very much interested in Dr. Stier's distribution chart.

About five years ago there was a great agitation in our state as to what Russian thistle was going to do. Russian thistle came in from the West, from the Panhandle district, and gradually drifter east. I pointed out to the members of the Board of Agriculture that it would not go east of Oklahoma City, because I had studied its growth in connection with the surface soils, with one of the gentlemen who was interested. We found that the Russian thistle never grew where there was not a peculiar sandy loam. We do not believe it will ever go into the eastern counties of Oklahoma. It extends forty miles west of Oklahoma. It first started with some seaweed that came over into South Dakota from Russia in 1882. It has not gone into Iowa, Indiana, Illinois, or Missouri, but it has gone west. The probability is, unless we are badly mistaken, that it will never go east because of the surface soil. It is like the juniper; it has to have a loam to grow in and the Russian thistle has to have a sandy loam.

DR. ALBERT H. ROWE, OAKLAND, CALIF.—I should like to ask Dr. Stier if he tests his patients with any of the pollens of cultivated flowers. I have found it helpful to test routinely the hay fever patient with the pollens of cultivated flowers to enable us to warn them against exposure to various flowers in the house or in gardens near their windows. Sometimes our poor results have been due to the pollens of different cultivated flowers to which they are sensitive.

We have pollen of over thirty different cultivated flowers that we have been using for two years, and their use has increased the relief we have been able to give to many of our patients. Positive tests have been found especially to chrysanthemum, coreopsis, marigold, daisy, calliopsis, dahlia, cosmos, rose, and California privet pollens, as well as many others.

DR. ROBERT L. BENSON, PORTLAND.—With regard to Dr. Stier's finding the dandelion pollen sensitization and also Dr. Balyeat's observation on it, we have had cases here in which there was no sensitization to any other composite plant that we could find, and in several districts where we have no ragweed of any type or Franserias either, for that matter.

The only way I can explain it is that children get it from the common habit of dusting their noses with dandelions, but I am not sure that this is of any significance. I have found three-plus or four-plus reactions with it and have treated with it, but I cannot see that it is if any importance in the treatment.

DR. JOHN P. HENRY, MEMPHIS.—I would like to ask Dr. Stier whether these patients who give positive reactions to dandelion have lived in other parts of the country, because, as Dr. Balyeat said, patients who react to dandelion will frequently give positive reactions to sunflower, goldenrod, and the ragweeds.

In Memphis, we frequently test patients who give strong reactions to Russian thistle. We ask the patient, "Have you lived in some part of the West?" They reply, "Yes," and usually give a district in which I know Russian thistle is present. Naturally, if they remain in our territory, we do not use Russian thistle in

treating them. I thought perhaps some of these patients who react to goldenrod and dandelion might have acquired their sensitivity while living in another part of the country.

DR. STIER.—Thank you, gentlemen, for your discussion. I appreciate Dr. Piness' correction on the matter of classification. I realize that we should use a uniform classification, otherwise we will not know where we are. When this paper is finally published, if Abrams' classification is the one we should use and is generally adopted, that is the one we shall use in the final publication.

I did not expect as much discussion on the dandelion as we had, but it is a definite factor in the mountainous district of Northern Idaho. I do not know very much about the coast district, but I do know that district in Montana. I think Dr. Foss, who published some of his work around Missoula, Montana, pointed out that same fact. These patients are invariably sensitive to the sages but few, if any, sages are found around Missoula.

DR. PINESS.—What do you mean by sages?

DR. STIER.—The *Artemisia tridentata, Artemisia vulgaris,* and so forth. They do not pollinate during the time that these patients have their symptoms, which commence when we are expecting the grasses to pollinate. They do not react to the grasses and in the case of several of these patients the only thing with which they have been treated is dandelion pollen.

Their symptoms occurred when the grasses were pollinating, which is early, and their symptoms did not extend into the time when the sagebrushes should be pollinating. The sages begin pollinating up in that country in July.

DR. PINESS.—Did not your dandelions continue into the same period?

DR. STIER.—They begin to throw their seeds about the first of July at the very latest. We are more or less forced to conclude that they are factors. I have a nurse at the hospital who has become sensitive to dandelion. We are treating her with dandelion extract and her symptoms have absolutely disappeared, returning only when too large a dose is given or too long an interval of time is allowed.

The brome grasses do produce a lot of pollen, as Dr. Piness has said, and the pigweeds also. We find that the red root pigweed, particularly, is a decided factor. Personally, I have seen quite a bit of Russian thistle around Omaha. I know it extends that far. I do not know about Iowa as I have never been there.

DR. PINESS.—Did you mean that tumbleweed produced a great deal of pollen?

DR. STIER.—I did not say tumbleweed. I mean the red root pigweed.

DR. PINESS.—Let us get this straight, because Durham and I think you are wrong on one of them and we do not know which one you are talking about. We do not want to go on record as saying that there is a great deal of pollen from one or the other.

MR. DURHAM.—I asked about the tumbleweed form of plant.

DR. STIER.—I cannot say as to that. The red root pigweed is the one that has most of the pollen.

MR. DURHAM.—*Amarantus retroflexus* produces very, very sparingly.

DR. STIER.—As to the cultivated flowers, we do not test regularly for them I have always contended that the air-borne pollens produce the symptoms.

I have noticed an interesting thing regarding the patients living in our territory. We routinely test for the various ragweeds in all of our patients. It is quite interesting to note the patients who come to our territory from the Middlewest where ragweed occurs. After they live in our territory a little while, they begin to show symptoms of sensitiveness to Russian thistle, and in that time the ragweed sensitization is gone. I have also noticed on several occasions that a patient who has given the history of having had symptoms in the Middlewest will develop a sensitization to Russian thistle in our territory.

Department of Reviews and Abstracts

Selected Abstracts

Trypsin and Ephedrin Dissolved in Gomenol as Therapeutic Agents in Allergic Conditions. Caulfield, A. H. W.: Canad. M. A. J. **20**: 498, 1929.

The author gives case reports in which the patients were materially benefited by the administration of the above-mentioned two substances. Trypsin, in large doses, was given in cases of multiple food sensitization where the food elimination or desensitization was difficult.

In bronchial asthma and hay fever, the use of ephedrin has met with marked success, in spite of an unfavorable cardiac, nervous effect in a limited percentage of cases. The bronchial instillation of gomenol in which ephedrin had been dissolved, met with additional success with the author, in that the cardiac nervous symptoms were reduced in one case which had responded to the injection of ephedrin with violent cardiac distress. Moreover, it was found in other instances, that the good effect on the asthma, presumably due to the ephedrin, was prolonged from about 2 to 6 days. This is a marked improvement on the duration of relief afforded by the injection of ephedrin alone.

The method employed was to instil into the trachea about 2.0 c.c. of ephedrin (from 1 to 1.5 per cent) in gomenol (10 to 20 per cent)—ephedrin alkaloid is weighed with aseptic precautions and sifted onto 50 c.c. of gomenol, which is then immersed for one hour in a water bath at 56° C.—by the supraglottic method, by means of a Yankhauer laryngeal syringe.

These two methods of treatment are presented by the author, not in the expectation that they may be of use to a large group of cases, but rather because they benefited selected cases where other methods were unsuccessful.

On the Question of the Pathogenesis of the So-called Ursol-Bronchial Asthma. Genkin, S., and Owtschinski, M.: München. med. Wchnschr. **76**: 916, 1929.

Ursols are artificial (anilin) dyes used in the dyeing of skins and furs. An occupational asthma has long been observed among workers in pelts dyed with ursol. In 1920, Curschmann and his coworkers, on the basis of their clinical and experimental work, gave the opinion that the asthma of workers in fur was anaphylactic in nature. The authors

have been unable to substantiate this theory. Thirty-one cases were selected where the asthmogenous factor clearly was ursol. In the majority of cases, besides typical attacks, eosinophiles in the blood or characteristic findings in the excreta were observed. In all phases of development of ursol asthma, pathologic symptoms of the air passages were present. Nevertheless, in this clinical material, the anaphylactic or allergic nature of ursol asthma could not be established according to the authors, because in no instance was a positive skin test to ursol obtained. Case reports are given in great detail.

The Surgical Treatment of Bronchial Asthma. Phillips, E. W., and Scott, W. J. M.: Arch. Surg. **19**: 1425, 1929.

It is still a matter of discussion whether the cause of asthmatic dyspnea may be: (a) spasm of the intrinsic muscles; (b) mucosal swelling; (c) abnormal secretion.

Whichever theory is adopted, the control lies, in part at least, in the extrinsic pulmonary nerves. This fact has given rise to the hope that nerve interruption might benefit the disease. In 1923, Kümmel performed a unilateral cervical sympathectomy in an attempt to relieve a severe case of bronchial asthma. In the following year, Kappes performed a vagotomy on the right side below the point of emergence of the recurrent laryngeal nerve. Immediately thereafter, operations on the extrinsic nerves of the lung became extremely popular. An attempt to estimate the results is made in this paper. More than 300 operations on the autonomic nervous system in asthmatics have been reported, many of which are considered inconclusive for lack of sufficient data or for a postoperative interval of sufficient length. Analysis of carefully followed and reported cases (six months was considered the minimal postoperative interval) showed:

(a) Failure in about one-half the cases.
(b) Varying degrees of improvement in the other half.
(c) A few brilliant cures in cases considered hopeless.

Successful results have been obtained by the interruption of the vagus alone and of the sympathetic alone. When the operation on one system has failed, results have sometimes, although less commonly, been obtained by interruption of the other system. The authors advise the initial severing of both systems at the posterior pulmonary plexus. They report in detail a case in which benefit was obtained over a period of eight months by this procedure. Such surgical interference, they submit to be in the experimental stage but advocate its use in certain severe cases where antiallergic and other medical measures have failed. In many asthmatic cases with a considerable degree of emphysema and fixation of the thorax, chondrectomy with destruction

of the perichondrium is advised by the authors before any operation on the autonomic nervous system.

Infantile Pyloric Obstruction. Cohen, M. B., and Breitbart, J.: Am. J. Dis. Child. **38**: 741, 1929.

Under infantile pyloric obstruction are classed both those cases where the obstruction is completely spasmodic and those where the origin is combined spasmodic and organic. Studied from an allergic point of view, the following points were considered:

1. Family history of allergy.
2. Presence of other allergic reactions in the patients either at the time of the pyloric obstruction or late in life.
3. The demonstration of a positive skin reaction to a specific allergen and the demonstration of a passive transfer.
4. Therapeutic testing by dietary change based on evidence obtained by the immunologic methods employed.

Analysis of the histories of 27 patients showed a familial allergic tendency in 40.7 per cent.

Allergic manifestations (eczema, asthma, urticaria, etc.) in one or more forms were observed in 44 per cent of these 27 patients before the age of twelve years.

Immunologic studies were made on 6 infants; on 4 at the time of the pyloric obstruction and on 2 later in life. In all of these cases positive skin reactions were obtained and in all but one, passive transfer could be demonstrated. Three case histories are given in detail. Upon the administration of atropine and change of diet, the pyloric symptoms disappeared. From the evidence presented it is shown that allergy may be present and may be demonstrated immunologically in cases of infantile pyloric obstruction and that the physiologic pathologic changes in these cases are similar to those in allergy.

It is suggested that patients with organic pyloric obstruction are probably sensitized in utero early in prenatal life; that repeated shocks occurring during prenatal life probably result in secondary hypertrophy.

Most cases of spasmodic pyloric obstruction, it is suggested, represent late intrauterine sensitivity with shock doses reaching the sensitized area after birth or infrequently before birth.

Coincident Allergic Symptoms in Bronchial Diseases and Rheumatism. Gehlen, H., and Otto, J.: Deutsche med. Wchnschr. **55**: 1964, 1929.

It came under the observation of the authors that in many patients rheumatic symptoms and bronchial diseases occurred simultaneously. The possibility was recognized that these might owe their appearance to a similar allergic factor. Previous reactions to skin tests led to the

hypothesis that this offending factor was a mould. Experiments were carried out upon 125 patients. Of these, 116 had rheumatic symptoms. Fifty-two of the original 125 cases presented bronchial complications. Intracutaneous skin tests with mould extracts showed:

Negative	32
Slightly positive	37
Positive	28
Strongly positive	28

These gave a total of 93 positive reactions. Subtracting from this number the 52 cases presenting bronchial complications, there remain 41 cases (38.1 per cent) in which the process leading to mould allergy is extra pulmonary. The supposition is that eventually the rheumatic symptoms are due to a mould intoxication. An extensive review of the literature reveals the fact that the growth of moulds has been observed in many organs of the body.

The authors conclude, not that chronic progressive rheumatism is an allergic disease due to moulds, but rather that both forms of disease, etiologically and allergically have many points of similarity, which suggest that they have their origin in a toxic process due to moulds.

Further experiments are being carried on for the substantiation of this work.

A Case of Dermatitis Venenata Due to Ephedrine. Scheer, M.: Arch. Dermat. and Syph. **20**: 641, 1929.

A case of a man aged forty-five with an acute dermatitis of the face and hands of two days' duration is reported. The entire face was bright red, swollen, and thickly covered with small vesicles. The lower lids, nose, and upper lip were edematous. There was much burning and itching. The dorsal surfaces of both hands were similarly affected, but here the vesicles were larger. No definite etiology was determined at the time. With local applications, the dermatitis subsided in from three to four days.

A second attack occurred following the use of ephedrine in oil as a nasal spray. This preparation was then identified as having been used just preceding the first attack.

Anaphylactic Conjunctivitis and Conjunctival Crises in Asthmatics. Vallery-Radot, P.: Blamoretier, P., and Stehelin, J.: Presse méd. **33**: 529, 1929.

The discussion concerns itself with certain types of noninfectious conjunctival crises which arise suddenly and disappear suddenly, leaving no trace. Certain of these crises are described as being clearly of an anaphylactic origin, such as the ocular symptoms familiar in hay fever. Somewhat more rare are the cases of conjunctivitis associated

with contact with animal proteins (horse dander, cat dander, etc.). Several such cases are described in some detail. Cases are also cited of conjunctival anaphylactic symptoms whose origin lies in contact with vegetable proteins. In all these cases of anaphylactic conjunctivitis through sensitization to animal or vegetable protein, the crisis is sudden and reaches its height in a few moments and presents the picture of ordinary conjunctival catarrh.

There is another class of conjunctival crises found among asthmatics which resembles those previously outlined but which differs in that the anaphylactic origin is not so clearly evident. In certain of these cases the ocular symptoms so predominate over the nasal symptoms that the coryza may pass almost unnoticed. Unless care is taken, such cases may be diagnosed as ordinary conjunctivitis of an infectious origin. They represent, however, the true equivalent of the crisis of bronchial asthma. Cases are reported in detail.

Heat and Effort Sensitiveness: Cold Sensitiveness: Relationship to Heat Prostration, Effort Syndrome, Asthma, Urticaria, Dermatoses, Noninfectious Coryza and Infections. Duke, W. W.: Arch. Int. Med. **45**: 206, 1929.

Duke discusses the very complex question of the heat regulating mechanism of the body. He then identifies the following illnesses as due at times to disorders of this mechanism: heat prostration, effort syndrome, noninfectious coryza, asthma, urticaria, and certain dermatoses. Allergic reactions to foreign substances may give rise to symptoms similar to those of sensitiveness to heat and cold; and, where the two conditions coexist, the symptoms may be heightened by the effects of either. In many persons adequate cause for heat and cold sensitiveness can be discovered. In others, no pathologic process can be found, but here a history of an acute febrile disease just antedating the onset of the illness often appears. During such disease the heat regulating apparatus works at an abnormally high level, and during convalescence there is a subnormal temperature in many cases. In the latter instance where the heat regulatory mechanism is working at a low level, Duke believes that a response to normal body temperature might simulate that normally caused by increased temperature and give rise to an unusually great loss of heat with a resulting fall in temperature. He states that it seems possible that under certain conditions the abnormal level at which the heat regulating mechanism works during a febrile disease or during convalescence is maintained and gives rise to abnormal responses to heat and cold for prolonged periods of time, or permanently.

Clinically, these patients run subnormal temperature curves. Several of these curves are shown in the text. In one patient, who had a generalized seborrheic dermatitis which had been present summer and

winter for years without remission, the temperature curve was subnormal, especially during the periods in which the eruption was active. Heat or effort made the condition definitely worse. However, when the body temperature was continuously maintained at a higher level by the use of B. coli, the skin lesions completely disappeared.

Another chart of a case of asthma due to cold sensitiveness is shown. Here, too, the temperature curve is constantly subnormal, excepting for temporary rises caused by exercise or a hot bath. During such times, the patient remained comfortable. If these measures were not taken, the patient was subject to asthma while running a low temperature. These attacks could be relieved immediately through exercise or the external application of heat. Several other similar cases are cited.

It is interesting to know that in testing a heat-sensitive patient by immersing the forearm in water at 42° C. with consequent production of symptoms, the same symptoms could be induced if a tourniquet were placed above the area of immersion. Moreover, such symptoms could be made to disappear by rubbing both forearms with ice, even with the tourniquet still applied. Duke believes that in such cases, symptoms of heat sensitiveness are in part a response to the sensation of heat.

As for treatment in heat-sensitive patients, they should be made to avoid undue effort and an environment wherein they are likely to be overheated. They do best in a dry, cool climate. On the other hand, a febrile disease almost always gives temporary or even permanent relief. This may also be secured through the prolonged use of colon bacilli parenterally injected.

Cold-sensitive patients can frequently gain tolerance for cold through the use of frequent cold baths, and this is advocated.

Serologic Investigations in Allergic Diseases in Man. DeBesche, A.: Acta path. et microbiol. Scandinav. **6**: 115, 1929.

The literature on passive transfer of sensitivity from one individual to another is reviewed at some length. This includes not only transfer from man to man but also from man to another species. Protocols are given of the passive transfer of sensitivity from one person to another in cases of asthma, urticaria, and Quincke's edema. Allergic antibodies can thus be shown in the serum of a patient suffering from allergy and these serum modifications, according to the author, must be considered as specific for these diseases and an essential factor in their pathology. It was furthermore shown that the sites for the passive transfer could be desensitized.

The author takes the stand that anaphylactic antibodies and allergic antibodies (the "atopic reagins" of Coca) are identical or very closely

related and not, as has been maintained, of an entirely different nature. His opinion is based largely upon the facts that (a) antibodies in serum sickness (an acquired and not an inherited condition) can be passively transferred; and (b) antibodies can be transferred passively from rabbit to man in cases of horse serum sensitivity. An instance of this is given. A rabbit was used which had been sensitized to horse serum and whose serum showed a high titer for precipitins to horse serum (1:20,000). A normal individual was chosen whose skin gave no reaction to the rabbit serum in salt solution. This same solution was injected intracutaneously in one spot on the subject's arm. On a second spot was injected serum in the same dilution and amount of a normal rabbit. A third spot received an injection of physiologic salt solution. Twenty-four hours later, 0.1 c.c. horse serum was injected in all three spots. On the site of injection of the serum of the rabbit sensitized to horse serum, a large wheal with hyperemia appeared. The other two sites showed negative reactions. Consequently, the close relationship between precipitins and reagins is apparent. This is not in conformity with some American opinions.

Respiratory Anaphylaxis (Asthma) and Ricin Poisoning Induced With Castor Bean Dust. Ratner, B., and Gruehl, H. L.: Am. J. Hyg. **10**: 236, 1929.

The attention of the authors was drawn to a type of occupational asthma occurring among workers in a castor oil factory. It was suggested that the asthma might be due to the inhalation of castor bean dust, commercially known as pomace. Positive skin tests to pomace were obtained among these workers. The present paper reproduces the specific clinical picture in the guinea pig under experimental conditions with the same materials which brought it about in human beings.

An extract was made from pomace obtained from the factory. Two series of experiments were run:

I. Experiments with guinea pigs exposed to the inhalation of pomace (castor bean dust).

II. Experiments with guinea pigs exposed to the inhalation of pomace from which a large part of the ricin had been removed.

Under Series I, there were three groups:

(a) Sensitization due to the inhalation of pomace. Two animals were exposed in an inhalation chamber to pomace for eight hours in short daily intervals from January 21, 1928, to February 2, 1928. After an incubation period of seventeen days, each pig was injected intravenously with 0.5 c.c. of pomace extract. Each showed profound anaphylactic symptoms.

(b) Ricin poisoning due to the inhalation of pomace. In this group, 21 animals were exposed to pomace from one to two hours daily for

varying intervals and showed varying degrees of dyspnea. Death occurred from one to nine days after the initial exposure. Autopsy showed the pathologic signs of ricin poisoning with some anaphylactoid manifestations.

(c) Respiratory anaphylaxis (asthma) and increased ricin tolerance due to the inhalation of pomace. In this group 18 animals were exposed for a total of eight hours over a period of three weeks. After an incubation period of thirteen to seventeen days, the animals were again exposed in the inhalation chamber and the majority showed unmistakable signs of respiratory anaphylaxis. Ten of these animals, however, died of ricin poisoning several days to two weeks after the last exposure. Of the remaining 8 which lived after showing symptoms of respiratory anaphylaxis, 3 were injected intravenously with 0.5 c.c. of pomace extract. Of these, 2 died in acute anaphylactic shock and the third showed definite anaphylactic symptoms; after recovery, it was killed for autopsy. When autopsied, none of the 3 animals showed evidence of ricin poisoning. Experiments were then carried out on the ricin toxicity of pomace extract by intraperitoneal and intravenous injections into normal controls. Death from ricin poisoning was readily distinguished from death induced by the anaphylactogenic elements in the pomace. Because one-half of the animals exposed to the inhalation of pomace died from ricin poisoning, further experiments were carried out with an extract of pomace from which as much ricin as possible was removed without removing too much of the soluble anaphylactogenic proteins. These experiments constituted Series II. From this series, it was shown that:

(a) Pomace was only partially dericinized. (Six controls injected with an alkaline extract died of ricin poisoning.)

(b) This partial extraction of ricin enabled the animals to inhale the pomace without developing ricin poisoning.

(c) Pomace does contain sufficient anaphylactogenic properties to induce respiratory anaphylaxis.

(d) A greater degree of immunity to ricin poisoning is established when animals inhale small amounts of ricin at each exposure.

The authors conclude that castor bean dust contains a primary toxic element-ricin, but that this and the anaphylactic element can be clearly differentiated.

Ricin death can be brought about in the guinea pig through the inhalation of castor bean dust and immunity can be obtained by the inhalation of smaller amounts. Sensitization in the guinea pig can be induced through the inhalation of castor bean dust, and respiratory anaphylaxis can be demonstrated in animals which have been thus sensitized. The authors assume that respiratory anaphylaxis in the guinea pig and bronchial asthma in the human being are related phenomena.